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MAMMALIAN TOXICOLOGICAL EVALUATION OF TNT WASTEWATERS

Volume II
Acute and Subacute Mammalian Toxicity of TNT and the LAP Mixture

Final Report

By

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2,4,6-trinitrotoluene (TNT); 1,3,5-trinitrohexahydro-1,3,5-triazine (RDX); wastewater; photolyzed LAP; pink water; toxicity; mammalian toxicity; acute toxicity; acute oral toxicity; eye irritation; skin irritation; skin sensitization; *in vitro* microbial mutagenesis; Ames test; mutagens; *in vivo* cytogenetics; enzyme induction; subacute toxicity; subacute toxicity in dogs; subacute toxicity

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The acute toxicity of TNT, RDX, LAP (1.6 TNT/1.0 RDX), and/or LAP(I) (photolyzed LAP: 0.032 TNT/1.0 RDX, 10% undegraded RDX) was determined in mammalian species. In male and female rats, respectively, the acute oral LD50s were: TNT, 1320 and 794 mg/kg; RDX, 71 and 470 mg/kg; and LAP, 574 and 594 mg/kg or lower, depending on particle size. In male and female mice, respectively, the LD50s were: TNT, 660 mg/kg (both sexes); RDX, <75 and 86 mg/kg; and LAP, 947 and 1131 mg/kg. LAP(I) was examined in mice only; the acute oral LD50s in males and females were: 585 and 684 mg/kg, respectively.

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19. KEY WORDS (Continued)

in rats; subacute toxicity in mice; anemia; testicular atrophy; uterine hypoplasia; hemosiderosis; SGPT; cholesterol; unscheduled DNA synthesis assay; UDS assay.

20 ABSTRACT (Continued)

LAP and LAP(I) produced conjunctivitis, iritis, and/or corneal opacity in rabbit eyes; the irritation was not totally reversed in unwashed eyes after 7 days and longer. The primary skin irritation index was 0.082 (virtually nonirritating) for LAP and 0.38 (mildly irritating) for LAP(I). In the maximization test, LAP and LAP(I) produced mild reactions in 67 and 70%, respectively, of the sites of guinea pigs challenged with the material; these values classify both as strong allergens.

In in vitro microbial assays using microsomal activation (Ames test), TNT was mutagenic. LAP was also mutagenic, and photolysis increased its mutagenicity. In contrast, in vivo cytogenetics studies on rat bone marrow extracts failed to detect an effect of either TNT or LAP on somatic cells. The discrepancy between these results is tentatively ascribed to experimental differences. In the UDS assay, positive responses were obtained for TNT without metabolic activation and for LAP with metabolic activation. Results for RDX were negative in either case.

The effects of repeated oral administration of TNT and of LAP were determined in 90-day studies in dogs, rats, and mice. Observations common to the three species treated with either test material were depressed body weight and/or weight gain and food intake, mild to moderate hemolytic anemia, enlarged spleens and (usually) livers, hemosiderosis of the spleen, and colored urine. Testicular atrophy in dogs and rats and hypoplasia of the uterus in rats were found in the LAP study. Dogs and rats also exhibited increased serum cholesterol (and possibly bilirubin) and decreased SGPT (except for LAP rats) but not SGOT--a unique observation, based on the literature. These findings implicate the peripheral circulation and the liver as targets for TNT and LAP. Neurological signs were numerous with LAP and included, in dogs, convulsions, ataxia, paresis of the hind legs, inactivity (followed by hyperactivity), and head-bobbing and/or -swinging. Numerous deaths occurred among LAP-treated rats and mice at the high dose, and one male and one female dog administered the high dose died early. Partial adaptation to the treatments was noted in some cases, but enzyme induction studies did not elucidate the metabolic nature of this process. Photolysis reduced the toxicity of LAP in repeated exposure experiments in rats. The results indicated that TNT was the principal--but not the sole--factor in the toxicity of LAP with repeated administration. Based on the results obtained, "no observable effect" levels for TNT and LAP in the subacute studies on the three species were: dog, 0.20 and 0.50 mg/kg/day for TNT and LAP, respectively; rat, 0.002 and 0.005% in the diet for TNT and LAP; and mouse, 0.005% in the diet for both materials.

19. KEY WORDS (Continued)

20 ABSTRACT (Continued)

An Acceptable Daily Intake (ADI) range of TNT for humans has been calculated from the toxicological data in these experiments to be 0.20 to 7.76 μg/kg. For LAP, the ADI range is 0.50 to 8.28 μg/kg. The calculated upper range for TNT and for LAP in water effluents were 6.3 to 245 and 16.2 to 268 μg/liter (ppb), respectively.

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EXECUTIVE SUMMARY

Under this contract from the U.S. Army Medical Bioengineering Research and Development Laboratory, SRI International conducted studies in mammalian species to determine the toxicity of 2,4,6-trinitrotoluene (TNT) and of a wastewater from TNT production. The wastewater was a representative mixture of TNT and 1,3,5-trinitrohexahydro-1,3,5-triazine (RDX), commonly referred to as LAP (load, assemble, and pack) wastewater. Specifically, the research was to determine the acute toxicity of TNT and both photolyzed and nonphotolyzed samples of LAP, conduct 90-day subacute oral toxicity (repeated administration) studies of TNT and LAP, assess the mutagenicity and cytogenicity of the materials, and perform enzyme induction studies on them.

The principal objective of the initial (acute) toxicity studies was to define the properties and the potency of the LAP mixture as a toxin. In these experiments, we determined the acute oral LD50 of TNT, RDX, and LAP in rats and mice and of LAP(I) in mice, the eye and skin irritation of LAP and LAP(I) in rabbits, the skin sensitization of LAP and LAP(I) in guinea pigs, and in vitro microbial mutagenicity of TNT, LAP, and LAP(I) in the Ames test. LAP was moderately toxic to rats and mice; in rats, the acute toxicity of LAP was between that of TNT and RDX, whereas in the mouse, LAP was less toxic than either component. Photolysis of LAP, to produce LAP(I), decreased its toxicity in mice. The relative acute toxicity of the test materials was, in descending order, in the rat: RDX > LAP > TNT; and in the mouse: RDX > LAP(I) > TNT > LAP.

In rabbits, LAP and LAP(I) were eye irritants [LAP(I) irreversibly] but were mildly or only slightly irritating to skin. They were classified as strong allergens by the criteria of Magnusson and Kligman in the skin sensitization test in guinea pigs.

In vitro mutagenicity experiments in Salmonella bacteria were conducted to determine whether microsomal preparations could activate TNT in the assay. TNT had previously been reported to have no mutagenic activity in the absence of metabolic activation. In the present work, however, the microsomal system did convert TNT to a mutagenic form, although high levels of the TNT were required in the assay. In light of correlations between mutagenic activity in Salmonella assays and carcinogenic activity in vivo, TNT should be considered to be a potential carcinogen, as are many other aromatic nitro compounds. LAP was also mutagenic, and photolysis increased its potency in the assay.

The subacute toxicity of TNT was evaluated in 90-day studies in dogs, rats, and mice. Dogs were administered TNT at 0.20, 2.0, and 20 mg/kg/day by capsule; rats received 0.002, 0.01, 0.05, and 0.25% and mice were given 0.001, 0.005, 0.025, and 0.125% TNT in the diet.

The most common observations among the three species were: depressed body weight and/or body weight gain and reduced food consumption (temporary with mice); mild to moderate anemia; alterations in organ weights, including enlarged spleens and (usually) livers; hemosiderosis of the spleen; and colored urine. In dogs and rats, increased cholesterol (and possibly bilirubin) and decreased SGPT levels were observed. The depression in SGPT without a corresponding effect on SGOT is a unique manifestation of toxicity that has not been reported in humans who have experienced TNT intoxication. The anemia, however, is of the hemolytic type, a salient feature of TNT toxicity, and is accompanied by higher serum bilirubin in dogs (and possibly in rats) and by lower serum Fe in dogs. The increase in cholesterol levels and decrease in SGPT implicate the liver as a target organ for TNT toxicity. Neurological signs were confined to inactivity and, on one occasion, nystagmus in the dogs. A rough order of susceptibility to the TNT treatment is: dog > rat > mouse.

The subacute toxicity of LAP was also studied for 90 days in dogs, rats, and mice. Dogs were treated at 0.50, 5.0, and 50 mg/kg/day by capsule; rats received 0.005, 0.05, and 0.50% and mice 0.005, 0.05, 0.25, and 0.50% LAP in the diet. Body weights, weight gain, and food intake were suppressed in all three species. A type of anemia similar to that observed with TNT was produced, the spleens were enlarged and hemosiderotic, and the urine was colored (red). In dogs and rats, testicular atrophy was observed, the livers were enlarged, and cholesterol and/or triglycerides were elevated in blood sera. Effects on the uterus were observed, the most clear-cut being hypoplasia of the uterus seen in the rats. Dogs and rats exhibited numerous neurological and other signs of toxicity, which were most severe in the dogs. These included convulsions, paresis of the hind legs, inactivity (followed by hyperactivity), ataxia, head-bobbing and/or -swinging, and diarrhea. At the highest dose levels for dogs, rats, and mice, mortality was appreciable (up to 50% or more).

Most of these findings suggest that TNT dominates the toxicity of the LAP mixture and that many of the differences are probably quantitative in origin since animals receiving LAP at the high dose received more TNT than those receiving the high dose of TNT alone. However, some differences cannot be so simply explained, such as the absence of an effect of LAP on cholesterol in dogs after 4 weeks (in contrast to TNT), the absence of an effect of LAP on SGPT in rats, and alterations in some organ weights and other clinical chemistry parameters that were different in the two studies. A noteworthy difference was the significant mortality in the LAP rat study; the TNT content of the LAP mixture was only slightly higher (0.32%) than the level used in the TNT study, but no TNT-dosed rats died. For these reasons, the toxicity of the LAP mixture cannot be ascribed exclusively to the TNT component.

No-effect levels for TNT and LAP in the dog were 0.2 and 0.5 mg/kg/day, respectively. In the rat and mouse, these levels were 0.002 and 0.005% TNT, respectively, and 0.005% LAP in each. However, the hemosiderosis in the spleens of rats at the 0.005% TNT level was more severe than in controls.

An Acceptable Daily Intake of TNT calculated by EPA-suggested guidelines to produce no likely toxic effects in humans ranged from 0.20 to 7.76 μg/kg of body weight, depending on the reference species, based on the "no observable effect levels" in the subacute studies. For LAP, that range is 0.50 to 8.28 μg/kg of body weight.

The calculated upper limit range for TNT effluent in water bodies was determined to be 6.3 to 245 μg/liter (ppb) and for LAP (i.e., TNT and RDX mixtures), 16.2 to 268 μg/liter (ppb).

To assess the toxicity of repeated exposures to LAP(I), a 28-day study in rats was conducted. The test mixture was added to the diet at 0.0, 0.003, 0.03, and 0.3% by weight; an additional group of animals fed 0.3% LAP in the diet served as a reference control. The LAP(I) produced few toxic signs, even at the highest dose. The responses noted were: a temporary suppression in body weight gain, a very mild anemia, and an increased frequency of lymphocytic foci detected in the liver and/or kidneys of several rats that had been receiving the high dose. In contrast, 0.3% LAP produced low body weights and weight gain, smaller kidneys and hearts, mild anemia, high serum cholesterol, hemosiderosis of the spleen, and discolored urine. On the basis of these comparisons, it was concluded that the irradiated mixture was less toxic than the unirradiated mixture when incorporated into the diets of rats. It therefore appears that photolysis increases the acute toxicity of LAP to animals and its mutagenic potential, but decreases the subacute toxicity (repeated exposures).

In vivo cytogenetic analyses of TNT and LAP were conducted on bone marrow extracts from rats. The results indicated that in this assay, neither material caused mutations, which is in contrast to results in the _in vitro_ microbial assay with TNT. Our hypothesis is that either rats ingested insufficient quantities of the compound to induce genetic damage, or the compounds were metabolically deactivated before reaching the bone marrow. Consequently, the question as to whether TNT or LAP would cause genetic damage to mammalian systems _in vivo_ is still unresolved.

Unscheduled DNA synthesis (UDS) assays were also conducted on TNT, RDX, and LAP. UDS is a form of repair synthesis in cell cultures exposed to the test agent that reflects primary DNA damage. The cell line used in the assay is derived from human fibroblasts. TNT gave a positive response in the assay when metabolic activation was not used, but LAP did so only in the presence of metabolic activation. The results with RDX alone were negative under any of the experimental conditions.

The capacity for TNT to induce (stimulate) TNT metabolism by the hepatic microsomal enzymes was investigated to attempt to explain the partial recovery of rats from some of the toxicologic manifestations. Phenobarbital was used as a positive control. Unlike phenobarbital, TNT exhibited a limited capacity to induce the microsomal enzymes. Neither TNT nor phenobarbital appeared to increase the metabolic disposition of TNT. Thus, the partial recovery from chronic TNT effects could not be explained on the basis of enzyme induction.

FOREWORD

The U.S. Army Medical Bioengineering Research and Development Laboratory (USAMBRDL), Fort Detrick, Frederick, MD, has been conducting a research program since 1973 for the purpose of developing the scientific data base necessary for recommending water quality criteria for compounds unique to the munitions industry. A water quality criterion (as defined by the amended Clean Water Act, 1977) is a qualitative or quantitative estimate of the concentration of a pollutant in ambient waters that, when not exceeded, will ensure a water quality sufficient to protect a specified water use. The criterion is a scientific entity based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility. Currently, a water quality criterion consists of two separate numerical limits, one for the protection of human health and the other for the protection of aquatic organisms. These numbers, when translated by the appropriate regulatory agency, can be the basis of enforceable discharge or effluent limitations in a point source discharge permit issued under the Clean Water Act.

Since a water quality criterion is to protect designated water uses, a diverse, multidisciplined research program was developed by USAMBRDL that includes "effects" studies on laboratory and domestic animals, wildlife species, aquatic organisms, plants, and economically important crops. In addition, extensive chemical and biological fate and persistence tests are conducted to provide information on the behavior of a pollutant in the aqueous environment. These kinds of data are especially useful for making site-specific translation of criteria into enforceable discharge limits.

This report represents a portion of the mammalian toxicology data base being developed by USAMBRDL on materials related to the manufacture, processing, handling, and disposal of trinitrotoluene.

PREFACE

All animal facilities used in conducting the research described in this report have been accredited by the American Association for the Accreditation of Laboratory Animal Care. Maintenance and research practices in the use of laboratory animals were conducted according to the principles and standards enumerated in the Guide for Laboratory Animal Facilities and Care (1972) of the National Academy of Sciences/National Research Council, and the revised 1978 Guide for the Care and Use of Laboratory Animals, USHEW, PHS, DHEW Pub. No. (NIH) 78-23, and the Animal Welfare Act of 1966 (Public Law 89-544), as amended by the Animal Welfare Act of 1977 (Public Law 91-579). Our facilities are inspected and licensed by USDA, APIS (License Numbers 93-B-19 and 93-26).

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This work was conducted in the Life Sciences Division under the direction of Dr. Gordon W. Newell, Director of the Toxicology Department, until his departure in July 1978, and thereafter by Dr. David C. L. Jones, the new director. The experimental work in toxicology was directed by Dr. James V. Dilley, Manager, Inhalation Toxicology Program, with the assistance of Dr. Charles A. Tyson, Senior Biochemical Toxicologist.

The analytical work was directed by Dr. Ronald J. Spanggord, Manager of the Bio-Analytical Chemistry Program. Dr. Vincent F. Simmon, Manager of the Microbial Genetics Program, was responsible for the *in vitro* mutagenesis assays. Dr. Ann D. Mitchell, Manager of the Biochemical Cytogenetics Program, was in charge of the cytogenetics studies. Mr. Douglas E. Robinson performed the unscheduled DNA synthesis assays. Dr. Chozo Mitoma, Director of the Biomedical Research Department, conducted the enzyme induction studies.

Dr. Daniel P. Sasmore, Director of Pathology, supervised necropsies, clinical chemistry laboratory testing done at SRI International, and histopathological preparations and performed the microscopic examination of tissues. Sandra J. Phillips supervised necropsies, and Barbara A. Kirkhart supervised the histology work.

Dr. Harold S. Javitz, Statistician, devised the statistical program for analyzing data. Mr. Lawrence J. Walter developed the computer programs and supervised tabulation of the data. Drs. Dilley, Tyson, and Javitz were responsible for analysis of the experimental data.

Technical assistance in the toxicology and analytical chemistry areas was provided by Susan M. Winslow, Elizabeth A. Rumple, Deborah K. Palmer, Neal E. Winslow, Sandra L. Green, David Chu, Sussan Dejbakhsh, Bradford Gibson, Rodney Keck, and Claire Ingersoll.

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INTRODUCTION

The U.S. Army Medical Bioengineering Research and Development Laboratory (USAMBRDL) has been directed to evaluate the potential hazard to living systems of wastewater discharges from munitions facilities. Of primary concern are the acute and subacute effects on mammalian systems of the combination of 2,4,6-trinitrotoluene (TNT) and 1,3,5-trinitrohexahydro-1,3,5-triazine (RDX), commonly referred to as LAP (load, assemble, and pack) wastewater, and of condensate wastewater, which comprises several different nitrotoluenes and related compounds in varying ratios. The ultimate goal of the toxicological part of the USAMBRDL program is to determine the responses of selected mammals to long-term exposure to the principal compounds in these wastewater discharges and to representative mixtures of the discharges. Information from these studies will aid USAMBRDL in developing the scientific data base necessary for assessing the hazards associated with these materials.

Under contract with USAMBRDL, SRI International undertook extensive chemical and toxicological studies, the objectives of which were to identify and quantitate the chemical components of LAP water and the photolytic changes they may undergo and to evaluate the toxicity of TNT and TNT-containing wastewater mixtures. Volume I describes the chemical studies conducted on these components and mixtures.[1] In this second volume are reported the results of the acute (Phase I) and subacute (Phase II) toxicological studies aimed at defining the toxicity of TNT and LAP.

The Phase I studies were acute oral LD50 determinations of TNT, RDX, and LAP in rats and mice and a sample of irradiated LAP [designated LAP(I)] in mice only; eye and skin irritation tests of LAP and LAP(I) in rabbits; skin sensitization tests of LAP and LAP(I) in guinea pigs; and <u>in vitro</u> mutagenesis assays of TNT, LAP, and LAP(I) in <u>Salmonella</u> bacterial strains (Ames test). The Phase II studies are 90-day subacute oral toxicity experiments with TNT and LAP in dogs, rats, and mice; a 28-day comparative study of the subacute oral toxicity of LAP and LAP(I) in rats; enzyme induction studies with TNT and LAP on rat microsomal systems; <u>in vivo</u> cytogenetics experiments on TNT and LAP with rat bone marrow; and unscheduled DNA synthesis (UDS) assays on TNT, RDX, and LAP.

The LAP used in these studies is made of 1.6 parts of TNT to 1.0 part of RDX by weight. Volume I describes how this ratio for toxicological testing was established. The ratio represents the hypothetical worst condition--no pollution abatement before wastewater discharge. TNT was tested concurrently with LAP because of the lack of quantitative

data on the toxicity of TNT itself in mammalian species and because of the need to assess to the degree possible the contribution of TNT to the overall toxicity of LAP. LAP(I) was tested because the LAP components undergo photolytic decomposition in the environment, and a necessary determination was whether this process increases or decreases the toxicity of LAP discharges. In addition to photolysis products, LAP(I) contains 10% unreacted RDX and 0.32% unreacted TNT by weight.

The report is divided into the following sections to facilitate compilation and reading: Part 1, the Phase I studies; Phase II studies are described in Part 2 (subacute TNT studies), Part 3 (subacute LAP studies), Part 4 [28-day LAP(I) studies], and Part 5 (cytogenetics, UDS, and enzyme induction studies).

PART I - ACUTE STUDIES ON TNT, LAP, AND LAP(I) (PHASE I)

INTRODUCTION

In Phase I we conducted experiments to determine the acute oral LD50s for TNT, RDX, and LAP in rats and mice, and LAP(I) in mice only; the skin and eye irritancy of LAP and LAP(I) in rabbits; the skin sensitization to LAP and LAP(I) in guinea pigs; and the mutagenicity of TNT, LAP, and LAP(I) in *Salmonella*. Corresponding skin and eye irritancy and skin sensitization tests of TNT were previously reported.[2]

PROCEDURES

Animals and Housing

Male and female Sprague-Dawley-derived rats and Swiss-Webster mice were obtained from Simonsen Laboratories, Gilroy, California. Albino guinea pigs of the Hartley strain were purchased from Hilltop Laboratories, Los Angeles, California. The supplier of the New Zealand White rabbits was LIT Rabbitry, Aptos, California.

All rodents were observed for a minimum of 1 week after their arrival to ensure that only healthy animals were used. They were kept in air-conditioned rooms (75 ± 5° F) with a relative humidity of 50 ± 10% and photoperiod of 12 hours. The rats were marked with felt pen stripes on their tails for individual identification and housed five to a cage in plastic cages with wire tops and Absorb-dri hardwood bedding; mice were housed in smaller plastic cages with wire tops and Absorb-dri bedding and identified by tail markings. The rodents were fed ground Purina Laboratory Chow. They were given deionized tap water *ad libitum* through an automatic water system using lixit valves. Because these were short-term experiments, neither feed nor water were analyzed for pesticide contaminants or chlorinated hydrocarbons.

Rabbits were housed in all-wire cages with wire bottoms and alfalfa pellets in pans below and were identified by cage cards. They were fed Purina Rabbit Chow and tap water *ad libitum* as described above. Their eyes were inspected carefully for clarity before the rabbits were used. Guinea pigs were housed one to a cage in clear plastic cages, identified by cage cards and fed Purina Guinea Pig Chow and water *ad libitum* in water bottles.

Part 1

Materials

2,4,6-Trinitrotoluene was obtained from E. I. duPont de Nemours & Co., Wilmington, Delaware. RDX was obtained from Holston Army Ammunition Plant, Kingsport, Tennessee. Each compound was found to be >99% pure by elemental and chromatographic analysis.

The following procedure was used to prepare LAP(I) for the mammalian toxicological evaluations.[1] Solutions of TNT and RDX were prepared individually in 55-gallon drums with polyethylene liners, and their respective concentrations were monitored by high-pressure liquid chromatography (hplc). Then the solutions were combined in the LAP ratio in another 55-gallon drum. TNT concentrations averaged 32 ppm, and RDX concentrations averaged 20 ppm in the combined solution. This solution was pumped through the four-unit photolytic reactor system at 60 to 100 ml/min. The photolysate was collected in a 55-gallon drum and acidified to pH 1.5; 3-liter portions were extracted with 1-liter portions of diethyl ether. The ether extracts were combined and rotary-evaporated for removal of the majority of the ether. The remaining extract was frozen in dry ice/acetone and lyophilized to a brown residue. When this reactor system is used with chemical photolysis end points of 0.1 ppm TNT ± 100% and 2.3 ppm RDX ± 100%, approximately 4 hours of irradiation time were found to be necessary to produce 1 g of material. When the water is lyophilized off, this residue contained 10% RDX and 0.32% TNT by weight, which was then designated LAP(I).

Test Methods

Determination of Acute Oral LD50s of TNT, RDX, LAP, and LAP(I)

The acute oral LD50s for each compound or mixture were determined in immature rats and/or mice. Animals were fasted overnight (for at least 16 hours) before they were dosed. Four or five dose levels were used, comprising 10 males and 10 females per dose.

The test material was administered in corn oil via stainless-steel oral-dosing needles. The compounds were weighed and then placed in graduated cylinders, to which sufficient corn oil was added to make the desired concentration. The mixture was stirred briefly and transferred to beakers. A magnetic stirring rod was placed in each beaker. Each beaker was wrapped in aluminum foil and then wrapped in parafilm. The material was stirred until dissolved or suspended uniformly in the corn oil (at least 24 hours). Suspensions were checked for lumps and then returned to the stirrer, where they remained throughout dosing. Controls received corn oil alone.

The animals were weighed before dosing, and each animal was dosed with a volume based on 1 ml/100 g of its body weight. After dosing, the animals were returned to their cages and allowed food and water freely.

The animals were observed for toxic signs and mortality 2 to 3 times a day for the first day, twice a day for 7 days, and then once a day until 14 days had elapsed. The time of death was recorded, as were toxic signs as soon as they were observed. (All observations were number-coded according to coded observation sheets.) Animals that died were examined for any gross pathological changes. Body weights were recorded on Days 7 and 14 for survivors.

The LD50s and confidence intervals for each compound or test mixture were calculated by a computer program based on the maximum likelihood method of Finney[3] (see Appendix A).

Determination of Eye Irritation of LAP and LAP(I) in Rabbits

A modification of the Draize method[4] was used for determining eye irritation in rabbits. Nine albino rabbits were used, and their eyes had no defects or signs of irritation prior to testing. LAP or LAP(I) powder (0.10 ml) was applied to the lower lid of one eye of each animal; the eyelids were gently held together for 2 seconds, and then the animal was released. In three animals, the test substance was not washed from the eyes; in three others, the eyes were washed after 30 seconds; the eyes of the remaining three were washed after 5 minutes. The eyes were scored for irritation and other ocular lesions after 1, 24, 48, and 72 hours, or until they were clear, and again after 4 and 7 days if necessary to assess reversibility, using the recommended scoring scale (Appendix A).

Determination of Skin Irritation of LAP and LAP(I) in Rabbits

LAP and LAP(I) were evaluated as skin irritants by occluded patch-testing on rabbits and assessed by the Draize method for identifying primary skin irritants.[5] Five or six healthy rabbits were used for each test.

Twenty-four hours before exposure, a large area on each rabbit's back was shaved. The shaved area was divided into quadrants, providing four exposure sites per rabbit. Just before the test mixture was applied, the upper left and lower right quadrants were lightly abraded in a tic-tac-toe pattern with a wire abrader that barely penetrated the stratum corneum; the upper right and lower left quadrants were left intact. LAP or LAP(I) (0.5 g) was placed over a 2-sq-inch area in each quadrant and immediately covered with gauze sponges (Johnson and Johnson Co.). Rolled gauze was wrapped around the rabbit's trunk, covering the gauze sponges, and rubberized cloth was then wrapped around the gauze and secured in place with waterproof tape. The patches were removed after 24 hours, and the reactions were examined for edema and erythema immediately and 48 hours later--i.e., 24 and 72 hours after the application of the test material.

The sites were scored according to the scale in Appendix A. A primary irritation index was calculated based on the combined readings from all test sites at 0 and 48 hours, divided by 4. Compounds producing combined averages (primary irritation indices) of 2 or less are considered as only mildly irritating, those with indices of from 2 to 5 are moderate irritants, and those with scores above 6 are considered severe irritants.

Determination of Skin Sensitization to LAP and LAP(I) in Guinea Pigs

Guinea pigs that weighed 300 to 500 g were treated with LAP or LAP(I) according to the method of Magnusson and Kligman.[6] Their method (the maximization test) entails induction in two stages: (1) intradermal injection of the test substance in Freund's Complete Adjuvant at two sites; the Adjuvant alone at two other sites; and the test material dissolved at the same concentration in corn oil at the two remaining sites on the backs of 10 guinea pigs; and (2) after 1 week, topical application of the test mixture in petrolatum over the injection sites (2 x 4 cm each site) under an occluded dressing for 48 hours. The animals are challenged topically with a 25% suspension or solution or with as high a concentration as possible of the test mixture in petrolatum 2 weeks after topical induction. The sites are evaluated for erythema and edema 24 hours after removal of the challenge patches and again 24 hours later. The scoring system and allergenicity ratings, based on the percentage of animals sensitized, are noted in Appendix A.

In Vitro Mutagenicity Testing

Salmonella Typhimurium Strains TA1535, TA1537, TA1538, TA98, and TA100

The *Salmonella typhmurium* strains used at SRI are all histidine auxotrophs by virtue of mutations in the histidine operon. When these histidine-dependent cells are grown on a minimal media petri plate containing a trace of histidine, only those cells that revert to histidine independence (his^+) are able to form colonies. The small amount of histidine allows all the plated bacteria to undergo a few divisions; in many cases, this growth is essential for mutagenesis to occur. The his^+ revertants are easily scored as colonies against the slight background growth. The spontaneous mutation frequency of each strain is relatively constant, but when a mutagen is added to the agar, the mutation frequency is increased 2- to 100-fold.

We obtained our *S. typhimurium* strains from Dr. Bruce Ames of the University of California at Berkeley.[7-11] In addition to having mutations in the histidine operon, all the indicator strains have a mutation (rfa^-) that leads to a defective lipopolysaccharide coat; they

also have a deletion that covers genes involved in the synthesis of vitamin biotin (bio$^-$) and in the repair of ultraviolet (uv)-induced DNA damage (uvrB$^-$). The rfa$^-$ mutation makes the strains more permeable to many large aromatic molecules, thereby increasing the mutagenic effect of these molecules. The uvrB$^-$ mutation decreases repair of some types of chemically or physically damaged DNA and thereby enhances the strains' sensitivity to some mutagenic agents. Strain TA1535 is reverted to his$^+$ by many mutagens that cause base-pair substitutions. TA100 is derived from TA1535 by the introduction of the resistance transfer factor plasmid pKM101. This plasmid is believed to cause an increase in error-prone DNA repair that leads to many more mutations for a given dose of most mutagens.[11] In addition, plasmid pKM101 confers resistance to the antibiotic ampicillin, which is a convenient marker to detect the presence of the plasmid in the cells. We have shown that TA100 can detect mutagens, such as benzyl chloride and 2-(2-furyl)-3-(5-nitro-2-furyl)-acrylamide (AF2), that are not detected by TA1535. The presence of this plasmid also makes strain TA100 sensitive to some frameshift mutagens [e.g., ICR-101, benzo(a)pyrene, aflatoxin B_1, and 7,12-dimethyl-benz(a)anthracene]. Strains TA1537 and TA1538 are reverted by many frameshift mutagens. TA1537 is more sensitive than TA1538 to mutation by some acridines and benzanthracenes, but the difference is quantitative rather than qualitative. Strain TA98 is derived from TA1538 by the addition of the plasmid pKM101, which makes it more sensitive to some mutagenic agents.

All the indicator strains are routinely checked for their genotypic characteristics (his, rfa, uvrB, bio) and for the presence of the plasmid. Cultures are then stored in 10% sterile glycerol at -80° C. For each experiment, an inoculum from the stock cultures is grown overnight at 37° C in nutrient broth (Oxoid, CM67). After stationary overnight growth, the cultures are shaken for 3 to 4 hours to ensure optimal growth.

Aroclor 1254-Stimulated Metabolic Activation System

Some carcinogenic chemicals, either of the aromatic amino type or polycyclic hydrocarbon type, are inactive unless they are metabolized to active forms. In animals and man, an enzyme system in the liver or other organs (e.g., lung or kidney) is capable of metabolizing a large number of these chemicals to carcinogens.[10,12-14] Some of these intermediate metabolites are very potent mutagens in the *S. typhimurium* test. Ames has described the liver metabolic activation system that we use.[12] In brief, adult male rats (250 to 300 g) are given a single 500-mg/kg intraperitoneal injection of a polychlorinated biphenyl, Aroclor 1254. This treatment enhances the synthesis of enzymes involved in the metabolic conversion of chemicals. Four days after the injection, the animals' food is removed but drinking water is provided *ad libitum*. On the fifth day, the rats are killed and the liver homogenate is prepared as follows.

Part 1

The livers are removed aseptically and placed in a preweighed sterile glass beaker. The organ weight is determined, and all subsequent operations are conducted in an ice bath. The livers are washed in an equal volume of cold, sterile 0.15 M KCl (1 ml/g of wet organ), minced with sterile surgical scissors in three volumes of 0.15 M KCl, and homogenized with a Potter-Elvehjem apparatus. The homogenate is centrifuged for 10 minutes at 9000 x g, and the supernatant, referred to as the S-9 fraction, is quickly frozen in dry ice and stored at -80° C.

The metabolic activation mixture for each experiment consists of, for 10 ml:

- 1.00 ml of S-9 fraction
- 0.20 ml of $MgCl_2$ (0.4 M) and KCl (1.65 M)
- 0.05 ml of glucose-6-phosphate (1 M)
- 0.40 ml of NADP (0.1 M)
- 5.00 ml of sodium phosphate (0.2 M, pH 7.4)
- 3.35 ml of H_2O.

Assays in Agar

To a sterile 13 x 100 mm test tube placed in a 43° C heating block, we add in the following order:

(1) 2.00 ml of 0.6% agar*
(2) 0.05 ml of indicator organisms
(3) 0.50 ml of metabolic activation mixture (optional)
(4) 0.05 ml of a solution of the test chemical.

For negative controls, we use steps (1), (2), and (3) (optional) and 0.05 ml of the solvent used for the test chemical. Because the majority of organic compounds are not sufficiently water-soluble--particularly at the higher concentrations--we routinely use dimethyl sulfoxide (DMSO). Other solvents that are occasionally used are water, ethanol, and benzene. For positive controls, we test each culture by specific mutagens known to revert each strain, using steps (1), (2), (3) (optional), and (4).

This mixture is stirred gently and then poured onto minimal agar plates.† After the top agar has set, the plates are incubated at 37° C for 2 days. The number of his^+ revertant colonies is counted and recorded.

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* 0.6% agar contains 0.05 mM histidine and 0.05 mM biotin.

† Minimal agar plates consist of, per liter, 15 g of agar, 50 g of glucose, 0.2 g of $MgSO_4 \cdot 7H_2O$, 2 g of citric acid monohydrate, 10 g of K_2HPO_4, and 3.5 g of $NaHNH_4PO_4 \cdot 4H_2O$.

RESULTS

Acute Oral LD50s of TNT, RDX, LAP, and LAP(I)

Table 1 lists the acute oral LD50s of TNT, RDX, and LAP in rats and mice and of LAP(I) in mice.

The acute LD50s of TNT were 660 mg/kg in both male and female mice and 1320 and 794 mg/kg in male and female rats, respectively. After dosing, the animals became inactive and developed tremors within 1 or 2 hours, followed by petit mal convulsions and death within 4 hours in some animals. Animals that survived the convulsions were still alive at 14 days postexposure. Red urine was noted in cages of both species within 60 minutes after dosing.

An experiment to determine the acute oral LD50 of RDX in rats and mice was conducted. The acute oral LD50 of RDX was 86 mg/kg in female mice. A value in male mice was not determined since at least 5 of 10 mice died at every dose level tested. In rats, an LD50 value of 71 mg/kg was obtained for males. For female rats, none of 10 died at the 50 mg/kg level and 9 of 10 died at the 75 mg/kg level. The acute LD50 lies between these values. Before death, the animals showed symptoms similar to those produced by TNT, but not as pronounced. Death occurred faster with RDX than with TNT at comparable doses. After a dose of 5.0 g RDX/kg, the rats and mice died in less than 5 minutes.

The acute oral LD50s of LAP were 947 and 1131 mg/kg in male and female mice, respectively, and 574 and 594 mg/kg in male and female rats, respectively. Thus, the mixture was more toxic to rats than to mice, but no appreciable difference in toxicity between sexes was apparent. All animals given a lethal dose of LAP died within 24 hours after dosing, after having convulsions of the grand mal type. The animals that survived the convulsions also survived the 14-day post-treatment observation period. The survivors were very aggressive, suggesting some behavioral effect from the treatment.

When the mixture was retested after more exhaustive dispersion in corn oil (48 hr instead of 24 hr as in Table 1), the acute LD50s in male and female rats were lower (281 and 317 mg/kg, respectively). These animals exhibited discolored urine, rough fur, depressed activity before death, and, at the highest dose (750 mg/kg), humped backs. Toxic signs disappeared in survivors within one week, but the sole survivor at the highest dose had rough fur throughout the observation period.

The acute oral LD50s of LAP(I) were 585 and 684 mg/kg for male and female mice, respectively. Thus, the irradiated mixture was more toxic to mice than unirradiated LAP. All deaths occurred between 0.5 and 1 hour after dosing. Inactivity, convulsions, and/or squealing preceded death. A few animals were observed to bite at the air or paw their mouths. Red urine or feces were common in dosed animals. Mice that survived showed no outward signs of toxicity other than ataxia, which disappeared within a few hours.

Eye Irritation of LAP and LAP(I) in Rabbits

Table 2 summarizes the eye irritation scores for rabbits treated with LAP powder. One hour after treatment, eye irritation was limited to a mild redness of the conjunctivae in the rabbits that had had the substance washed from the eye 30 seconds and 5 minutes after treatment. The eyes that had been washed 30 seconds after treatment had zero scores at 24 hours, and the eyes that had been washed 5 minutes after treatment had zero scores after 7 days. The unwashed eyes had mild to moderate redness and swelling of the conjunctivae and a moderate discharge 1 hour after treatment. They were unchanged at 24 hours, but the discharge had diminished by 48 hours and had reached zero by Day 7. However, on Day 4, corneal lesions appeared in all the eyes that had not been washed, and one rabbit had developed opalescent areas in less than one-fourth of the cornea and in about half of the iris; that condition persisted through Day 7. The unwashed eyes of the other two rabbits had cleared in that time.

Table 3 summarizes the eye irritation scores for rabbits treated with the LAP(I) powder. The test material caused a moderate conjunctivitis in the eyes of all rabbits, washed or unwashed. The condition appeared within 1 hour of instillation and was accompanied, in some cases, by mild iritis.

In the group whose eyes were washed with water 30 seconds after instillation, two of the three rabbits still had iritis at 24 hours, but after 48 hours the condition had cleared in all three eyes. One of the rabbits in this group died on the third day of the test. At necropsy, the animal was found to have an exudate from the left (treated) eye and from the anus, moderate diffuse emphysema of the lungs, marked diffuse white spots on the liver, and hepatic coccidiosis. The animal was slightly autolyzed. Cause of death was not ascertained.

Corneal opacity was seen at the 24-hour reading in the unwashed eyes and in those eyes washed 5 minutes after instillation. This condition persisted in two of the three unwashed eyes for more than 30 days. In the group whose eyes were washed 5 minutes after instillation, all eyes were normal (scores of zero) by 15 days.

Skin Irritation of LAP and LAP(I) in Rabbits

Table 4 summarizes the scores recorded during the skin irritation tests of LAP on rabbits. Erythema was observed on 3 of 12 abraded areas, in contrast to 1 of 12 intact sites. The erythema cleared totally in all sites after 72 hours (48 hours later). The primary irritation score for the LAP mixture was 0.082.

Table 5 summarizes the scores recorded during the skin irritation tests of LAP(I) on rabbits. Distinct erythema was recorded at the application sites on two of the six rabbits upon removal of the patches [24 hours after application of LAP(I)]; these sites had cleared 48 hours later. Very slight edema was recorded at the sites on two of the test animals at the latter reading (72 hours after application). There was no pronounced difference between abraded and intact site scores. The primary irritation score calculated for the LAP(I) mixture was 0.38.

Skin Sensitization to LAP and LAP(I) in Guinea Pigs

Table 6 presents the individual scores for the guinea pigs treated with LAP. One guinea pig died overnight after challenge. Visual examination of that animal revealed no evidence of a strong allergic response to treatment. Considering the mildness of the response to treatment in the remaining animals, we ascribed the death to stress, which is not uncommon among guinea pigs in the sensitization test. No severe reactions (scores greater than 2) were observed with LAP in any of the other nine guinea pigs, and the redness observed at 24 hours had disappeared after 48 hours in all but one animal.

The percentage of guinea pigs responding to the treatment was 67%. By the criteria of Magnusson and Kligman[6] (Appendix A), the LAP mixture would be classified as a strong allergen.

Table 7 presents the individual scores for the guinea pigs treated with LAP(I). Although all of the reactions to LAP(I) were mild (scores of 1), they persisted for 48 hours. The percentage of guinea pigs responding to the challenge was 70%.

In Vitro Mutagenicity Testing

In a previous project,[15] we reported that no mutagenic activity was observed with TNT or RDX at their limits of aqueous solubility in *Salmonella typhimurium* or *Saccharomyces cerevisiae* D3. We also observed that at pH 7, 50% and 100% photolyzed and at pH 9, 100% photolyzed LAP were mutagenic in assays with *S. typhimurium*.

In the current study, we examined the mutagenic activity of TNT in the *Salmonella* microsome assay. The TNT was dissolved in dimethyl sulfoxide so that considerably more material could be added to each petri plate. Results of a representative assay are presented in Table 8. TNT increased reverse mutation rates, as indicated by a dose-related increase in mutants, in *S. typhimurium* strains TA1537, TA1538, TA98, and TA100 both in the presence and in the absence of the liver homogenate metabolic activation system (S-9 mix). Toxicity and mutagenicity were reduced by the S-9 mix.

The results of the Ames test on LAP and LAP(I) are presented in Tables 9 and 10. The test strains used were the same as above with and without metabolic activation. LAP was unequivocally positive only at the highest dose (5000 μg) tested with or without metabolic activation, and then in only three of the five strains (TA1538, TA98, and TA100). LAP(I) was positive in four of the strains (with or without metabolic activation) and marginally so in the fifth (TA1535). The response increased in a dose-related fashion and was apparent in some strains (TA1538, TA98, and TA100) at concentrations as low as 5.0 μg per plate. LAP(I) was clearly more mutagenic than LAP.

DISCUSSION AND CONCLUSIONS

Acute Toxicity of TNT, RDX, LAP, and LAP(I)

In rats, the acute oral LD50 for TNT is 1320 mg/kg for males and 794 mg/kg for females. The acute LD50 of RDX is 71 mg/kg in male rats and approximately that value in females. The LAP mixture has an acute oral LD50 of 574 and 594 mg/kg in males and females, respectively. These values--as well as the values obtained when LAP is dispersed for a longer period in the corn oil diluent (281 and 317 mg/kg, respectively, after 48 hours of mixing)--are between those for TNT and RDX, suggesting that in rats the two components of LAP act additively but in a mutually exclusive manner.

In mice, the acute oral LD50 of TNT is 660 mg/kg in both males and females, and that of RDX is <75 mg/kg in males and 86 mg/kg in females. Since the acute oral LD50s of the LAP mixture are 947 and 1131 mg/kg in male and female mice, respectively, the toxicity of LAP in this species is less than that of either of its components. This may result from interference in the production of metabolites responsible for the toxicity or from inhibition of absorption of the test materials. No difference in sensitivity to TNT, LAP, or RDX between sexes was evident, except for the higher LD50 obtained for TNT in the male rats.

The LD50s for TNT and RDX may be compared with other values reported in the literature. For TNT, Lee et al.[2] found acute oral LD50s of 1010 and 820 mg/kg for male and female rats, respectively. Schneider et al.[16] reported that when rats were given 50 mg of RDX in DMSO per kilogram of body weight, 20% died. They cautioned that the acute oral toxicity varies with particle size and with the nature of the solvent. Large particles, because of their decreased absorption in the gut, were less toxic. With the same RDX particle size and 1% methyl cellulose, all animals dosed with 100 mg RDX/kg of body weight died, whereas none died when this solvent was not used. These variations in particle size and solubility, even with the exhaustive efforts we have made to solubilize RDX (stirring for at least 24 hours), probably are responsible for the inability to obtain precise values for LD50s of RDX in all cases (Table 1). Although such values can be obtained, the expense would probably not be justified for the objectives of this study.

The LAP(I) mixture has an acute oral LD50 of 585 mg/kg for male mice and of 684 mg/kg for female mice. These values indicate that the irradiated LAP wastewater has greater toxicity than LAP itself. This result was opposite to what we had expected on the basis of aquatic tests. In those tests, the acute toxicity of the unirradiated and irradiated LAP was determined in four different species of fish and four invertebrate species.[17] Irradiated mixtures (with >50% TNT degradation) were invariably less toxic than the unirradiated LAP mixture. Because of the difference between the results of the mammalian and aquatic toxicity testing, a second test of LAP(I) was conducted in mammals--a modified subacute study of LAP and LAP(I) in the rat. The results of that study are described in Part 4.

Eye Irritation of LAP and LAP(I) in Rabbits

LAP caused no prolonged irritation in rabbits whose eyes were washed 30 seconds or 5 minutes after administration. It did cause a delayed reaction in the eye of one of three rabbits in the no-wash group, and the irritation persisted after 7 days. The lesion was characterized as an opacity of the cornea, which obscured about half the iris and was coupled with mild iritis. On this basis, LAP should be considered as an eye irritant. TNT alone did not cause eye irritation in rabbits.[2]

The reported development of cataracts in humans exposed to TNT is possibly relevant.[18-21] Determining whether repeated administration of LAP to the eye produced the lesion in rabbits was beyond the scope of this study. The mechanism of cataract formation is unknown, but a recent report on studies of diabetes implicates increased sugar concentrations in the blood as being a major factor in cataract formation.[22] The possibility that oral administration of TNT might produce cataracts by elevating serum glucose must also be considered. Consequently, particular attention should be paid in subacute or longer term studies to examinations of the eye for this effect, using blood glucose determinations as a possible early indicator of cataract formation.

Conjunctivitis, iritis, and corneal opacity were observed within 24 hours of instillation of LAP(I) in the eyes of most of the rabbits. These effects cleared in those eyes that were washed 30 seconds after administration and were clearing in those washed 5 minutes after administration. In eyes that remained unwashed, the conjunctivitis and corneal involvement persisted for 32 days; the corneal damage was judged to be irreversible in at least one of the three eyes. LAP(I), like LAP, is an eye irritant, and is apparently capable of causing irreversible damage to this organ.

Skin Irritation of LAP and LAP(I) in Rabbits

LAP has a primary skin irritation score of 0.082 in rabbits. This score is almost negligible (less than 2 is mildly irritating); therefore, LAP should be considered as virtually nonirritating to rabbit skin. In contrast, TNT is a mild irritant.[2]

LAP(I) has a primary skin irritation score of 0.38 in rabbits and on that basis is classified as a mild irritant. This score was slightly higher than that obtained with LAP, suggesting that the photolyzed mixture is more irritating to the skin.

Skin Sensitization to LAP and LAP(I) in Guinea Pigs

LAP causes a dermal reaction characteristic of hypersensitivity, according to the maximization test of Magnusson and Kligman.[6] In this test, LAP produced reactions in 67% of the animals; thus, it would be

classified as a strong allergen. This is not surprising because TNT and other nitrotoluenes are known to cause dermatitis in animals and man.[14,18,21]

The classification of LAP and LAP(I) as allergenic agents might be defined more precisely if we were to test 25 animals, as recommended in the Magnusson-Kligman procedure, as a follow-up. However, the value of performing a second test on more animals is questionable at this time. Although this method is probably the one most frequently used in animal testing, considerable dissatisfaction with it has been expressed. In 1977, the FDA and Consumer Product Safety Commission issued independent requests fo_ proposals to develop an improved, more predictive sensitization test method for animals. Therefore, we recommend awaiting the outcome of these investigations before deciding whether any additional work needs to be done to define the allergenicity response of LAP and LAP(I) in animals.

In Vitro Mutagenicity Testing

Because the Salmonella strains we use have endogenous aromatic nitro reductase enzyme(s), the activity that we observed possibly is high relative to the potential hazard of TNT. However, it should be noted that many aromatic nitro compounds have been shown to be mutagenic and carcinogenic.[7] Therefore, in view of the correlation between mutagenic activity in Salmonella assays and carcinogenic activity, TNT should be considered to be a potential carcinogen.

LAP and LAP(I) both produced increases in the number of revertants in several of the Salmonella strains used to assay for mutagenic potential. LAP tested positively in strains TA1538, TA98, and TA100 and LAP(I) did so in these strains plus TA1537. The effect of these mixtures on the other strains was equivocal. The addition of a microsomal metabolizing system to the plates during incubation had no pronounced effect on the results with either test mixture.

Although both LAP and LAP(I) were considered mutagenic on the basis of the assay results, LAP(I) was clearly much more potent in this [illegible]ect than LAP. LAP(I) produced an increase in revertants in more [illegible]ins than did LAP and at much lower concentrations (5.0 μg vs 5000 μg for LAP). It may be concluded that irradiation substantially increases the mutagenic potential of LAP. Since the percent content of unreacted TNT is much lower in LAP(I) than in LAP, the test results suggest that irradiation produces decomposition products that are more po[illegible] mutagens than TNT.

Table 1

ACUTE ORAL LD50s OF TNT, RDX, LAP, AND LAP(I)

Test Material	LD50*			
	Mouse		Rat	
	Male	Female	Male	Female
TNT	660 (524-831)	660 (574-758)	1320 (955-1824)	794 (602-1047)
RDX	< 75†	86 (8-124)	71 (56-85)	50-75†
LAP	947 (707-1094)	1131 (946-1344)	574 (482-658)	594 (502-678)
LAP(I)	585 (472-680)	684 (568-841)	--	--

* Each value is the LD50 and 95% confidence limits (milligrams per kilogram). For details of calculation, see Appendix B.

† Estimated from raw data; insufficient data in lethal range for computer use.

Table 2

EYE IRRITATION OF LAP IN RABBITS

Washing Time*	Total Scores† for Three Eyes: 1 Hour	24 Hours	48 Hours	72 Hours	4 Days	7 Days
No wash						
Cornea	0	0	0	0	25	30‡
Iris	0	0	0	0	5	5
Conjunctivae	36	30	12	10	14	0
Total	36	30	12	10	44	35
Wash 30 sec after treatment						
Cornea	0	0**				
Iris	0	0**				
Conjunctivae	16	0**				
Total	16	0				
Wash 5 min after treatment						
Cornea	0	0	0	0	0	0
Iris	0	0	0	0	0	0
Conjunctivae	18	14	4	0	12††	0
Total	18	14	4	0	12	0

* Three rabbits per group.

† Maximum possible score for three eyes by Draize method at any one reading is 330 (Appendix A).

‡ This score was in one rabbit only; there was corneal involvement and the iris was slightly red (score of 1). Scores for the other two rabbits' eyes were zero.

** Rabbits were observed again but not scored (were unchanged) at 96 hours.

†† Scored on the weekend by a different technician. Scores were 1 for redness, chemosis, and/or discharge (A + B + C = 2; see Appendix A for scoring scale) for each treated eye in this group.

Table 3

EYE IRRITATION OF LAP(I) IN RABBITS

Washing Time*	Total Scores† for Three Eyes After:												
	1 Hr	24 Hr	48 Hr	72 Hr	96 Hr	168 Hr	240 Hr	360 Hr	18 Days	21 Days	25 Days	30 Days	32 Days
No wash													
Cornea	0	40	45	40	50	35	20	20	15	15	20	20	20
Iris	10	0	10	10	10	10	5	0	0	0	0	0	0
Conjunctivae	34	50	48	44	32	22	18	10	6	8	4	2	2
Total	44	90	103	94	92	67	43	30	21	23	24	22	22
Wash 30 sec after treatment													
Cornea	0	0	0										
Iris	0	10	0										
Conjunctivae	20	18	6	‡									
Total	20	28	6										
Wash 5 min after treatment													
Cornea	0	15	25	20	5	0	0	0					
Iris	5	5	15	5	0	0	0	0					
Conjunctivae	32	42	28	16	12	14	4	0					
Total	37	62	68	41	17	14	4	0					

* Three rabbits per group.
† Maximum possible score for three eyes by Draize method at any one reading is 330 (Appendix A).
‡ Rabbit E-5 died before 72-hr reading; this rabbit had the only non-zero score at 48 hr.

Table 4

SKIN IRRITATION OF LAP IN RABBITS

Animal No.	24-Hour Readings* of Erythema Intact		Abraded	
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	1	0	1	1
6	0	0	0	1
Average total score	0.08		0.25	
Combined score	0.33			

Primary irritation score = 0.33 ÷ 4 = 0.082

* 72-Hour readings were zero at each site.

† No edema was observed at any site.

Table 5

SKIN IRRITATION OF LAP(I) IN RABBITS

Animal No.	24-Hour Reading* Erythema & Eschar Intact	24-Hour Reading* Erythema & Eschar Abraded	24-Hour Reading* Edema Intact	24-Hour Reading* Edema Abraded	72-Hour Reading* Erythema & Eschar Intact	72-Hour Reading* Erythema & Eschar Abraded	72-Hour Reading* Edema Intact	72-Hour Reading* Edema Abraded
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	2	0	0	0	0	0	1	1
4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	1	0
6	2	2	0	0	0	0	0	0

Average erythema and edema (intact sites) = 0.25.

Average erythema and edema (abraded sites) = 0.13.

Primary irritation score = 0.38.

* Scores in columns are for both sites.

Table 6

SENSITIZATION OF GUINEA PIGS TO LAP*

Animal No.	Scores at 24 Hours After Challenge: Erythema	Scores at 24 Hours After Challenge: Edema	Scores for Erythema at 48 Hours After Challenge
1	Died		
2	0	0	0
3	1	0	0
4	1	0	1
5	2	0	0
6	0	0	0
7	1	0	0
8	0	0	0
9	2	0	0
10	1	0	0
Percent Positive:	67	0	0

* Concentration of LAP in Freund's Complete Adjuvant and in corn oil for intradermal injection was 3%. Topical concentration of LAP in petrolatum for induction and for challenge was 20%.

Table 7

SENSITIZATION OF GUINEA PIGS TO LAP(I)*

Animal No.	Scores for Erythema at 24 Hours After Challenge†	Scores for Erythema at 48 Hours After Challenge†
1	1	1
2	1	1
3	1	1
4	0	0
5	1	1
6	1	1
7	0	0
8	0	0
9	1	1
10	1	1

Percent Positive: 70

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* Animal Nos. 1 through 5 and 6 through 10 were dosed at 2% and 1% of LAP(I) in petrolatum, respectively, in the induction step. The concentration was reduced because the high viscosity made LAP(I) in the adjuvant difficult to inject. The concentration for challenge was 25% LAP(I) by weight in petrolatum.

† No edema was observed.

Table 8

IN VITRO ASSAYS WITH SALMONELLA TYPHIMURIUM

2,4,6-TRINITROTOLUENE

Compound	Metabolic Activation	Micrograms of Compound Added per Plate	Histidine Revertants per Plate				
			TA1535	TA1537	TA1538	TA98	TA100
Negative control	-		29	12	10	30	127
	+		15	12	24	48	138
Positive controls							
β-Propiolactone	-	10	149				
9-Aminoacridine	-	100		812			
2-Nitrofluorene	-	10			1345		
AF2	-	0.1				259	938
2-Anthramine	-	2.5	34	14	8	44	139
	+	2.5	100	46	350	375	742
2,4,6-Trinitrotoluene	-	10	21	8	18	41	130
	-	50	19	11	37	51	164
	-	100	21	6	63	93	209
	-	500	15	40	127	255	678
	-	1000	0	0	0	5	0
	-	5000	0	0	0	0	0
	+	10	8	13	30	50	160
	+	50	7	15	28	42	184
	+	100	13	7	23	36	216
	+	500	10	9	25	64	410
	+	1000	15	48	83	200	1115
	+	5000	0	0	0	0	0

Table 9

<u>IN VITRO</u> ASSAYS WITH <u>SALMONELLA TYPHIMURIUM</u>

LAP

Compound	Metabolic Activation	Micrograms of Compound Added per Plate	Histidine Revertants per Plate				
			TA1535	TA1537	TA1538	TA98	TA100
Negative control (DMSO)	-		21	7	15	27	97
	-		14	9	15	27	131
	+		12	8	17	29	101
	+		13	9	19	33	100
Positive controls							
Sodium azide	-	0.5	147				250
	-	0.5	159				316
9-Aminoacridine	-	50		102			
	-	50		100			
2-Nitrofluorene	-	0.1			855	427	
	-	0.1			921	375	
2-Anthramine	-	1.0			15	29	
	+	1.0			178	105	
	-	2.5	9	7			109
	+	2.5	149	84			1195
LAP - 14 June 1978	-	1	6	7	15	12	101
	-	5	7	12	3	19	116
	-	10	17	12	9	19	98
	-	20	8	7	13	21	125
	-	50	14	5	8	30	112
	-	100	17	6	25	33	102
	-	500	18	12	78	65	139

Table 9 (Concluded)

Compound	Metabolic Activation	Micrograms of Compound Added per Plate	Histidine Revertants per Plate TA1535	TA1537	TA1538	TA98	TA100
LAP - 14 June 1978	-	750	26	9	86	72	135
	-	1000	16	14	62	93	164
	-	5000	27	20	398T*	421	603
	+	1	3	15	16	25	80
	+	5	9	6	26	31	104
	+	10	3	4	19	15	99
	+	20	7	3	18	29	78
	+	50	8	5	16	27	100
	+	100	8	9	20	38	102
	+	500	7	14	16	38	102
	+	750	8	12	36	34	96
	+	1000	13	12	25	48	90
	+	5000	24	24	196	178	451

* T = toxic.

Table 10

IN VITRO ASSAYS WITH SALMONELLA TYPHIMURIUM

LAP(I)

Compound	Metabolic Activation	Micrograms of Compound Added per Plate	Histidine Revertants per Plate				
			TA1535	TA1537	TA1538	TA98	TA100
Negative control (DMSO)	-		21	7	15	27	97
	-		14	9	15	27	131
	+		12	8	17	29	101
	+		13	9	19	33	100
Positive controls							
Sodium azide	-	0.5	147				250
	-	0.5	159				316
9-Aminoacridine	-	50		102			
	-	50		100			
2-Nitrofluorene	-	0.1			855	427	
	-	0.1			921	395	
2-Anthramine	-	1.0			15	29	
	+	1.0			178	105	
	-	2.5	9	7			109
	+	2.5	149	84			1195
LAP(I) - 9 June 1978	-	0.1	26	9	14	26	137
	-	0.5	14	6	41	25	115
	-	1.0	15	3	50	51	96
	-	2.0	19	16	74	56	116
	-	5.0	18	15	158	131	174
	-	10.0	14	39	371	223	200

Table 10 (Concluded)

Compound	Metabolic Activation	Micrograms of Compound Added per Plate	Histidine Revertants per Plate TA1535	TA1537	TA1538	TA98	TA100
LAP(I) - 9 June 1978	-	50.0	19	196	1263	995	543
	-	75.0	19	244	1583	1281	697
	-	100.0	33	320	1797	1712	749
	-	500.0	51	457	2075	2606	911
	+	0.1	7	3	14	26	92
	+	0.5	7	9	19	41	93
	+	1.0	8	7	16	28	110
	+	2.0	8	6	24	43	87
	+	5.0	13	12	68	45	113
	+	10.0	5	21	89	63	127
	+	50.0	14	57	309	301	330
	+	75.0	19	66	712	483	462
	+	100.0	26	97	775	611	490
	+	500.0	42	541	2207	2215	1273

PART 2 - SUBACUTE ORAL TOXICITY STUDIES ON TNT (PHASE II)

INTRODUCTION

This section describes the results of the 90-day subacute oral toxicity studies of TNT in dogs, rats, and mice. These studies were performed (1) to define toxic symptoms arising from repeated oral doses of TNT and to identify the target organs or systems; (2) to establish a dose-response relationship where possible; (3) to establish no-effect levels for exposure of the species to TNT; and (4) to provide guidelines for establishing the dose levels to use in the chronic studies. The reversibility of any adverse effects was assessed in groups allowed to recover for 4 weeks after discontinuation of treatment with TNT.

PROCEDURES

Studies in Dogs

Housing and Maintenance

Forty American Kennel Club (AKC)-registered beagles from Marshall Laboratory Animals, North Rose, New York, were used in these experiments. The dogs were 5 months old on receipt at SRI. They were identified by ear tattoos, inspected when received, and numbered with metal tags on chain collars and by cage cards. The dogs were quarantined for a minimum of 3 weeks; those that were found to be unhealthy were returned to the supplier and replaced by healthy animals before the study commenced.

The dogs were housed two to a run or singly in covered outdoor runs that are protected from inclement weather by a roof, walls, and side curtains. Each dog was fed 400 ± 5 g of dry Wayne Bite-Size Kibble® daily. The food was placed in the food pans immediately after the dogs were dosed. The food was picked up for reweighing 2 to 3 hours later. (The dogs had been trained on this feeding schedule while they were in quarantine.) Food consumption was determined daily for each run, 5 days per week. Food consumption/animal/day was calculated from the sum of the food consumed by dogs in each group over this 5-day period divided by the sum of the number of days each dog in the group survived (5 x number of dogs/group if none died prematurely). On weekends, the dogs received approximately the same amount of food, but the unconsumed food was not weighed.

Part 2

Treatment Protocol

The beagles were divided into three treatment groups and one control group consisting of five males and five females each. All treated beagles were dosed daily by capsule. At the end of 4 weeks, one male and one female from each group were killed and a second male and female from each were set aside for recovery. The latter two animals were killed 4 weeks later (after 4 weeks of treatment and 4 weeks of recovery). The remaining dogs were continued on treatment for a total of 13 weeks, at which time two males and two females from each group were killed. The remaining dogs were withdrawn from further treatment and allowed to recover for 4 weeks before they were killed.

TNT was mixed with predetermined amounts of lactose (U.S.P.) powder for ease of handling. The TNT/lactose mixture was then weighed under a ventilated hood on a Mettler P162 balance to ± 0.01 g, on the basis of the weight of the dog to receive the dose, and placed in 1/8-oz. gelatin capsules. Control dogs were given the same amount of lactose powder in capsules. Dose levels administered were 0.0, 0.2, 2.0, and 20.0 mg TNT/kg of body weight. Periodically, samples were analyzed for TNT content by reverse phase hplc using methanol:water (60:40) as eluent.[1] The compounds and capsules were stored in the dark in a refrigerator until use. The dogs were dosed between 9:30 and 11:30 a.m. each day.

Tests

All dogs were observed daily during capsule administration and feed weighings, and unusual signs were recorded. They were weighed once a week, and food consumption was recorded 5 days a week.

Hematology and clinical chemistry determinations were performed on blood samples from surviving animals at 0, 4, 8, 13, and 17 weeks. Approximately 10 ml of blood was drawn from the jugular vein of each dog via a 20-gauge, 1.5-inch needle fitted into a 10-ml syringe. Two milliliters of fresh blood were immediately transferred to a 2-ml Vacutainer containing EDTA anticoagulant for blood counts (CBCs, including hemoglobin and hematocrit). The remaining 8 ml of blood was centrifuged after clotting for 10 minutes at 2000 rpm in an IEC International Universal Model UV centrifuge. The serum was transferred by syringe to an additive-free, 10-ml Vacutainer and refrigerated. The whole blood and serum samples were delivered on the same day to Peninsula Medical Laboratory (Menlo Park, California) for analysis. Appendix A describes the analytical methods used by that laboratory, which is a fully accredited, State-licensed facility. Urinalysis methods on urine samples taken from dogs are also described in Appendix A.

At sacrifice, each dog's brain, heart, liver, kidneys, spleen, gonads, thyroid, and adrenals were weighed immediately and the absolute weights were recorded. A computer program was used to calculate organ-to-body weight and organ-to-brain weight ratios from these data. All body and organ weights, hematology, and clinical chemistry data were compiled and evaluated statistically as described in Appendix A.

All tissues or representative sections were fixed in 10% neutral buffered formalin and saved for histopathological analysis. Other tissues examined grossly and microscopically were the aorta, bone, bone marrow (smears only), colon, cholecyst, duodenum, epididymis, esophagus, eye, ileum, jejunum, lung, lymph node, sciatic nerve, pancreas, parathyroid, pituitary, prostate, salivary gland, seminal vesicles, skeletal muscle, spinal cord, stomach, trachea, urocyst, uterus, and vagina. The thymus was also examined unless it was unidentifiable because of atrophy. The methods used to prepare and examine slides are described in Appendix A.

Studies in Rats

Housing and Treatment Protocol

One hundred and five male and 105 female Sprague-Dawley (outbred) rats, approximately 6 weeks old, were obtained from Simonsen Laboratories, Gilroy, California, on the same day. They were quarantined for 1 week to ensure that only healthy animals were used in the study. The animals were assigned three to a cage alternatively with two to a cage in the order they were received off the truck. As the cages were filled, they were assigned to groups in the following sequence: controls, low dose, mid dose, and high dose, each group (20 males and 20 females) being filled before the next was started. Individual animals were identified with cage cards and ear punches.

Diets were prepared by mixing TNT with powdered Purina Laboratory Chow* in a U.S. Stoneware ball mill to form a stock mixture. The stock mixture was diluted with Purina chow to make the 0.25% high dose diet using a Hobart H-600-T rotary mixer. The remaining diet levels were prepared in descending order of concentration: 0.05%, 0.01%, and 0.002% TNT by weight by diluting aliquots of the preceding diet level with powdered chow. The control diet was unaltered powdered Purina Laboratory Chow (0% TNT). The diets were placed in hanging feeders in the cages and added to or changed weekly as the supply warranted. All diets were kept refrigerated until used, and fresh diets were prepared and administered biweekly. Stability of the TNT was determined by hplc after extraction of feed samples with dichloromethane; TNT was unchanged after 4 weeks.

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* Rodent Laboratory Chow 5001 (formerly Laboratory Chow 5001).

Part 2

The schedule for sacrificing the animals was as follows. At the end of 4 weeks of treatment, five males and five females from each group were killed, and five additional males and five females from each group were placed on recovery (no treatment) for 4 more weeks before they were killed. The remaining rats were continued on treatment for a total of 13 weeks. At the end of that period, half the rats were killed and the other half were allowed a 4-week recovery period before they were killed. The rats were fasted for 16 hours before sacrifice.

Tests

Each rat was weighed weekly, and food consumption was determined weekly per cage by the difference between initial and final feeder weights. These differences were summed for all cages per group and divided by the number of animal days for that group during the week. (Animal days = the number of the animals in the group times the sum of the number of days each survived during the week.) All test animals were observed daily, and unusual signs were recorded.

Blood and serum samples were collected at each sacrifice time; the samples were refrigerated and delivered on the same day to Peninsula Medical Laboratory for analysis. Immediately before sacrifice, each rat was anesthetized with chloroform and blood was drawn directly into a 10-ml syringe after puncture of the heart with a 20-gauge, 1.5-inch needle. Two milliliters of fresh blood was immediately transferred to a 2-ml Vacutainer containing EDTA for determination of CBCs, including hemoglobin and hematocrit. Sera were prepared from the remaining blood in the same manner as for dogs.

Immediately after sacrifice, the brain, heart, liver, kidneys, spleen, and gonads (males only) were weighed. The absolute organ weights were recorded, and weight ratios were calculated using a computer program. All tissues were fixed for histopathological examination in the same manner as for dogs. Other rat tissues that were so examined were the adrenal, aorta, bone, bone marrow, cecum, cervix, colon, duodenum, epididymis, esophagus, eye, ileum, jejunum, lung, lymph node, sciatic nerve, ovary, pancreas, pituitary, prostate, salivary gland, seminal vesicle, skeletal muscle, skin, spinal cord, stomach, thymus, thyroid, trachea, urocyst, uterus, and vagina. The mammary glands and parathyroids were also examined, but in fewer instances. Any tissues of unusual appearance noted at necropsy were examined histopathologically.

Studies in Mice

One hundred male and 100 female Swiss-Webster mice (15-20 g in weight) from Simonsen Laboratories were used. The protocol and test methods for this experiment were the same as those for rats, with the following differences:

(1) Mice were housed five to a cage.

(2) Dose levels were 0.0, 0.001, 0.005, 0.0025, and 0.125% TNT by weight.

(3) Feeders in the cages were of the covered variety.

(4) Individual mice were identified with cage cards and by yellow spots of dilute picric acid solution on their fur. The markings were as follows in each cage: #1, one spot on the head; #2, one spot at the base of the tail; #3, one spot on the head plus one spot at the base of the tail; #4, a stripe from head to tail; #5, no spot.

(5) No serology was done because of the small amount of blood available from a mouse. Blood samples were diluted with normal saline to provide enough volume for hematologic analysis.

The methods of drawing blood, of euthanasia, and of storing and transferring blood samples to Peninsula Medical Laboratory were the same as for rats. Weekly body weights and food consumption were determined in the same manner as for rats. The same organs and tissues were examined grossly and microscopically as in the rat, with the addition of the cholecyst in the case of the mouse.

RESULTS

Studies in Dogs

Observations

Loose mucoid stools and diarrhea were frequently observed among the animals that received TNT at the 20 mg/kg/day level. The only overt sign of possible neurological effects was inactivity in males, a condition that lasted for periods of several days. On one occasion nystagmus was seen in one of the males. By Week 12, the three remaining males became inactive, however, and this inactivity persisted until treatment was terminated.

A further observation was that the 20-mg/kg TNT dose produced an orange-tinted color in the dogs' urine, particularly among the females. This began on the sixth day and lasted as long as TNT was administered.

One male dog (A3-39) treated with 20 mg/kg/day became moribund and was killed during the twelfth week. This dog had suddenly stopped eating, so it was emaciated. Its kidneys, liver, and spleen were enlarged, weighing 76, 750, and 100 g, respectively--50 to 75% greater than the weights for the same organs from control dogs killed at 13 weeks. At necropsy, swelling was noted in the left upper cerebral

hemisphere of A3-39, the lung was congested and dark in color, roundworms were in the duodenum (these had been observed during the ninth week and occasionally in the stools of this dog at other times), and the lymph nodes were hemorrhagic and reactive. Dog A3-39 had marked anemia and almost no mature myeloid cells. Almost all (93%) of the remaining white cells were lymphocytes. Changes in the clinical chemistry profile of the dog included an elevated cholesterol level--318 mg % (controls, 130 ± 9 mg %)--and a slightly increased alkaline phosphatase level of 205 mU/ml (controls, 95 ± 20 mU/ml).

Body Weights

Tables 11 and 12 present the mean body weights for males* and females determined weekly during the 13-week treatment periods. No statistically significant effects on body weight were detected. All male and female groups lost 0.2 to 0.6 kg during the first week, except for females at the 20-mg/kg/day level; they lost 1.4 kg. Except for males and females given the highest dose and females given the intermediate dose, all groups had recovered and were gaining weight by the first sacrifice (Week 4). We attribute these initial changes in body weight principally to the stress or anxiety caused when administration of capsules began. From Weeks 5 to 13, the maximum overall change in any group was 0.6 kg, indicating a very stable period. However, in both males and females given 20 mg/kg/day, a slight downward trend in body weights was apparent after Week 9, which in the case of males coincided with the development of inactivity. However, the control dogs also lost weight during this period, and because of this there is no clear relationship of this trend to the treatment.

Tables 13 and 14 present the weekly differences in body weights of the treated dogs. While both males and females at the 20 mg/kg/day level lost more weight during Week 1 than did other groups, only the female body weight differences were statistically significant ($p < 0.05$). Females at the 2.0 mg/kg/day level lost weight overall during the first four weeks; their failure to gain weight during Week 4 was statistically cited ($p < 0.05$).

Tables 15 through 18 present the body weights for dogs treated with TNT for 4 or 13 weeks and then observed for 4 more weeks untreated. The female given 2.0 mg/kg/day lost weight up to Week 4 and recovered thereafter (Table 16). Since this transition coincided with the dog's

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* The data for the males that received the high dose (20 mg/kg/day) on Week 12 are pooled values that include the dog killed during Week 12 of treatment and the other two surviving males. The body weight of the killed dog was 9.9 kg at sacrifice. Hematology and clinical chemistry data on these males were similarly pooled.

removal from treatment, the possibility exists that TNT was responsible for its weight decrease. The female given the 20-mg/kg/day level lost far more weight (2.0 kg) than any other animal during the first week. Again, the weight loss may be partly due to the treatment and the recovery may be due to adaptation to and withdrawal from the treatment.

An interesting observation was that during recovery, two males and one female given the high dose lost weight. In the dogs treated for 13 weeks, the reversal in body weight appeared to start during the treatment period (Week 10). Those animals had loose stools occasionally throughout the recovery period. The male became noticeably thin during Week 15 and was very thin by Week 16 (Table 17). This dog had roundworms in its stools during Days 56 to 60 and occasionally afterwards. The female remained outwardly healthy except for the appearance of loose stools occasionally, which was not considered abnormal.

The male given the high dose for 4 weeks lost weight only during recovery. During this period, it had sore feet and diarrhea during Week 6. The condition so worsened that the dog was treated with Azium® and Bicillin® for 3 days during week 7 and with Bicillin again the following week. Although the dog still had swollen front feet during Week 8, its condition was improving on the last day.

In summary, a TNT dose of 20 mg/kg/day does produce body weight loss, and the 2.0 mg/kg/day level possibly affects the weight of some dogs. These effects are temporary initially; but, as the result of the female at 2.0 mg/kg/day indicates, they can be more long-lasting. The lower body weights in the dogs at the 20-mg/kg/day level late into the study--regardless of whether the dogs continued on treatment--is of concern since it may reflect a delayed onset of toxicity, and this effect therefore may be treatment-related.

Food Consumption

Tables 19 and 20 summarize food intake data for all groups over the 13-week treatment period. The average male beagle consumes between 300 and 400 g of food daily, and females consume slightly less. Based on this criterion, the food intake in the high-dose (20 mg/kg/day) groups was appreciably lower than in the other test groups and the controls during the first week and was slightly lower during the second week also. Food intake for every group was lowest during the first week, when all dogs experienced a weight loss, and it improved over the next 2 to 3 weeks. Thereafter, there were no pronounced trends or differences that might be attributable to the treatment.

Part 2

Organ Weights

Tables 21 through 24 present organ weights and organ weight ratios for dogs sacrificed while on treatment. At 4 weeks, the most significant findings were the enlarged spleen in the male and the enlarged liver in the female at the 20-mg/kg/day level of TNT. These organ-to-body weight and -brain weight ratios were also high. After 13 weeks, the hearts of the females at the 2.0-mg/kg/day level appeared larger on the average, in terms of absolute weight and the two ratios, but these values were not out of line compared with those of other females (see Table 22). At the 20-mg/kg/day level, the weights of both livers and spleens (and the ratios) were high compared with those of controls in both sexes (marginally so for the two females). At 13 weeks, the adrenal weights and adrenal-to-body weight ratios were highest in the dogs receiving the highest dose. The kidneys were enlarged and the hearts were smaller in the males also after 13 weeks of treatment with TNT at 20 mg/kg/day, and dog A3-39 had small testes (15 g).

Tables 25 through 28 present the organ weight data and ratios on dogs allowed to recover. At the 8-week sacrifice (4 weeks of treatmer and 4 weeks of recovery), only the dogs that had received the high dose were killed. This was an economical measure, considered justified because pathological effects at lower levels had not been observed after 4 weeks and because the animals at these levels in the recovery stage appeared to be healthy. In the male, some organs were smaller than expected (e.g., thyroid and heart). Since the heart-to-brain weight ratio was also low, the smaller heart may be related to the treatment. Although the condition of this male was not satisfactory, we nevertheless concluded that organ weights were not indicative of the factors that contributed to this condition. The female, although healthy, did have an enlarged spleen and high spleen-to-body weight and -brain weight ratios that are noteworthy.

After 13 weeks of treatment and 4 weeks of recovery, the male at the 2.0 mg/kg/day level had a somewhat large kidney and the kidney-to brain ratio was the greatest of all males observed to that point. We observed slight interstitial foci of lymphocytes in the kidneys of the female, although the kidneys were not enlarged. The foci of lymphocytes were not observed in the male at the high dose. At the highest dose level, no alterations in organ weights were apparent.

Hematology

Tables 29 through 40 present the values from hematological determinations made on dogs before and during treatment and recovery. When started on study, the animals had all the outward appearances of being healthy and were quite energetic. However, the first report from Peninsula Medical Laboratory (initial values) and reports almost throughout the study indicated that the percentage of band cells was high. Such a condition might arise from the use of medication (not

the case here), infection (coupled with high WBC, but see below), or misreading of the slides by an untrained technician. We checked the uric acid and creatinine levels (indicators of enhanced protein turnover) and found them to be normal for these animals. K^+ ion concentration and WBC levels were also normal. After 13 weeks of treatment and 4 weeks of recovery, band cells dropped inexplicably back to the normal range. Peninsula Medical Laboratory representatives reassured us that only an experienced technician worked on our samples over this period. Thus, the anomaly appears singular relative to the rest of the hematology and clinical chemistry data; although we have no explanation for it, the test result does not appear to be related to the general health of the animals.

Tables 31 through 36 show that both males and females at the 20-mg/kg/day level of TNT had pronounced anemia, characterized by decreases in RBC, Hgb, Hct, and MCHC and increased MCV. The anemia was most marked during the first 4 weeks and improved slightly thereafter; recovery in the females was dramatic between Weeks 8 and 13, except for MCV and MCHC values. The only other finding that might be related to the treatment is the tendency toward low PMN values after 4 and 13 weeks at the high dose compared with controls (not observed, however, at Week 8).

For the dogs sacrificed after a 4-week recovery period (Tables 37 through 40), we detected leukopenia in the male exposed for 4 weeks to the high dose of TNT (the dog that was losing weight at termination). RBC, Hgb, and Hct were high in the control and low in the female exposed to 0.2 mg/kg/day TNT and sacrificed at 8 weeks. The exposed animal was small but otherwise healthy and alert. The females that received the higher doses had more normal hematological values, so we attributed these observations to the variability expected when one animal only constitutes a group. The percentage of PMN cells of the high-dose female (but not of the male) was also low.

After 13 weeks of treatment and 4 weeks of recovery, the male at the 20-mg/kg/day level of TNT showed lingering signs of anemia (low RBC, Hgb, and Hct), leukocytosis, and high PMN levels--possibly a reflection of an increase in formation of new cells to compensate for the anemia. The condition of the dog on the high dose had been deteriorating up to sacrifice, and it was thin and had pigmented macrophages in its liver (possibly hemosiderosis). The female at the high dose, which had also lost some weight but was otherwise visibly healthy, also had high WBC characterized by marked granulocytosis. In addition to macrophages in its liver, that female had hemosiderosis of the spleen and vaginitis. The prolonged treatment at this level might have increased the propensity for infection, but the histopathology and band cell levels--correlative evidence for an infection--were normal and there was no appreciable increase in lymphocyte counts.

Clinical Chemistry

Tables 41 through 48 present the blood chemistry data for dogs on treatment. After 4 weeks, the females at the 0.20-mg/kg/day level of TNT showed significantly low SGPT, but this value is not outside the normal range values we have observed for SGPT. At the 2.0-mg/kg/day level, both sexes had high uric acid (in both t- and r-tests). The males also had increased alkaline phosphatase activity, which had been observed initially in this group (Table 41) and therefore was not related to treatment, and low iron, which might be related to the treatment. At the 20-mg/kg/day treatment level, cholesterol was increased significantly in both sexes (marginally in the r-test, either unflagged or A-flag) and SGPT was markedly decreased (C or D in the r-test). In addition, bilirubin was elevated (statistically significant in at least one test) in both sexes relative to controls, and iron was low (significantly so for males). Thus, cholesterol, SGPT, bilirubin, and iron appear to be altered by TNT treatment at the level of 20 mg/kg/day.

After 8 weeks of treatment, dogs in the low- and intermediate-dose groups had several altered clinical chemistry parameters. Phosphorus in males at the 2.0-mg/kg/day level was high but not abnormally so. Creatinine, uric acid, electrolyte balance, and SGPT showed notable differences in females, even at the high dose; these differences were attributable either to atypical control values or to normal group-to-group variation. The effects on cholesterol (high), bilirubin (high), SGPT (low), and iron (low) noted at 4 weeks in the high-dose animals were seen again at 8 weeks. Although the changes were not statistically significant in several instances, they were considered to be treatment-related. Linear trend analysis confirms this in the case of cholesterol and SGPT (Table C-4 in Appendix C).

After 13 weeks, triglyceride in males and creatinine in females at the low and intermediate doses were statistically different from the control values. In the former case, no consistent trend in these values was evident and values for triglycerides of 10 to 20 mg % were common in this study. In the latter case, the lower creatinine level for the controls was responsible for the difference. At the high-dose level, cholesterol remained noticeably high (not significant statistically), bilirubin was high ($p < 0.05$ for males only, but D for each sex in the r-test), SGPT was very low (significant at either $p < 0.01$ or $p < 0.05$), and iron was low (not significantly so).

The globulin levels for males at the 20-mg/kg/day level showed an interesting response with time. In contrast to controls and to males at the lower treatment levels, this measure gradually increased over 13 weeks, leading to a decreased A/G ratio. The effect was observed in females with up to 8 weeks of treatment but not thereafter. It appears that the treatment (nonspecifically) enhanced the synthesis of globulins. Additional studies might be justified (in conjunction with the 6-month chronic study of TNT in dogs now planned) to identify and quantitate the class(es) of globulins affected.

Tables 49 through 52 present clinical chemistry values for dogs removed from treatment after 4 weeks of recovery. The clearest result was the absence of an effect on SGPT in any of the four high-dose recovery dogs; suppression of SGPT was clearly reversible. Cholesterol tended to remain high at this level but not greatly so, and the significance was obscured by occasional high values at other levels (e.g., the female dog at the 0.20-mg/kg/day level in Table 50). Bilirubin was unchanged except in one female sacrificed at 8 weeks (4 weeks of treatment and 4 weeks of recovery), in which case the value was on the high side. Iron values also tended to be high in the dogs sacrificed at 8 weeks, suggesting possible overcompensation by the hematopoietic system for the anemia that occurred during treatment. Only the value for the male on the high dose sacrificed at 8 weeks seemed notably high. Other differences were the electrolyte balance of the high-dose male at the 8-week sacrifice (a normal value that appeared high contrasted with the others at this sacrifice time), the high triglyceride value for the control female, and zero bilirubin, which we suspect are test errors.

In summary, TNT treatment altered cholesterol, bilirubin, SGPT, and iron at the 20-mg/kg/day level. Some effects at lower levels, such as on uric acid and iron at the intermediate level after 4 weeks, may be treatment-related, at least in the case of iron. All these effects are reversible.

Urinalysis

Urine samples were taken aseptically from the bladders of all dogs on the TNT study at sacrifice. The samples were evaluated for specific gravity, pH, albumin, sugar, appearance, WBC, RBC, epithelial cells, bacteria, and crystals (see Appendix A for definitions and methods).

The most significant observation was the dark amber color of the urine from dogs at the 20-mg/kg/day level after 4 and 13 weeks of treatment; this was seen in none of the other dogs, including those at this treatment level that were allowed 4 weeks of recovery. The coloration was possibly due to the presence of a metabolite of TNT, which is at present unidentified. In addition, urine from half the dogs on the high dose of TNT had specific gravities of 23 to 47, and the two male dogs on continuous treatment for more than 4 weeks had traces of protein (in one case, a 1+ score) in their urine.

Dog A3-39, the male that was moribund and killed in Week 12, had dark-amber urine, a WBC score of 2-6, a 2+ for calcium oxalate crystals, and a faint trace of albumin in its urine.

Histopathology

Except for the high-dose male, A3-39, the dogs in the control and treatment groups generally were in good nutritional condition, and no gross alterations were observed at sacrifice. Table 53 summarizes the microscopic lesions found in dogs killed after 4 weeks of treatment. No clear treatment-related effects were observed, except possibly the hemosiderosis in the spleen of the female. This may have resulted from the pronounced anemia observed in these animals at sacrifice. The observation of alveolar collapse and dilation in the high-dose male is not singular and has been observed occasionally in other dogs at other treatment levels and in controls.

Tables 54 and 55 summarize the microscopic findings in dogs killed after 13 weeks of treatment (including the male A3-39). Both high-dose males and one of two females had liver lesions and enlarged livers. Several other observations that might be related to the treatment were restricted to the high-dose male A3-39. These were hyperplasia of the bone marrow, extramedullary hematopoiesis, and hyperplasia of the prostate. Since alveolar collapse and testicular atrophy were noted in control males at this sacrifice, we cannot ascribe these effects unambiguously to the treatment. The presence of a nematode parasite in the duodenum of dog A3-39 may indicate a complication causing some of the pathologic effects observed in that dog. All other lesions in males or females found at this sacrifice time were so distributed among the groups and the groups were so small that we cannot attribute their occurrence to the treatment.

Tables 56 through 58 list the microscopic lesions found in dogs allowed a 4-week recovery period. Only the two dogs at the 20-mg/kg/day level were examined. After 4 weeks of treatment and 4 weeks of recovery, slight focal nephrocalcinosis was seen in the kidneys of both dogs, and the female had congestion of the spleen. These effects were not seen in the dogs killed after 13 weeks of treatment and 4 weeks of recovery. In the latter case, parenchymal lymphocytes were seen in the liver of the male at the high dose. The female had a modest solitary focus of alveolar histiocytosis of the lung (not seen in the other females), moderate hemosiderosis of the spleen, and slight diffuse vaginitis. These effects may reflect incomplete recovery of these dogs after the more prolonged exposure to TNT.

Studies in Rats

Observations

Rats were treated with TNT levels of 0.002, 0.01, 0.05, and 0.25% (w/w) in their diets. Five rats of each sex were killed at each sacrifice time; none died prematurely in any of the groups.

No outward signs of toxicity were apparent in rats during the study. Urine from both sexes at the highest treatment levels (0.05 and 0.25%) was red on Day 2, and this continued until sacrifice. In males and females subjected to treatment at 0.01%, red urine appeared on Day 50 and the color persisted until sacrifice. When the rats were removed from treatment and allowed a recovery period, the red coloration disappeared from the urine within 15 and 16 days after 4 and 13 weeks of treatment, respectively.

Body Weights

Tables 59 and 60 give the weekly mean body weights for males and females during the 13-week treatment period. Compared with controls, the males (Table 59) receiving 0.25% TNT in the diet exhibited significantly lower body weights every week ($p < 0.01$). The ratio test indicated that the computer-calculated interval for the mean for this high-dose group was 10 to 20% lower than that of the control group during the first 12 weeks and 20 to 35% lower during Week 13; during the last week, the high-dose males apparently failed to continue growing. All other male treatment groups exhibited low body weights compared with controls. These differences were apparent at 4 weeks, when sets of animals were killed and others were set aside for recovery. Thus, these differences in body weights apparently are attributable to differences in the subpopulations of the groups continued on treatment rather than to the treatment itself.

At both the 0.05 and 0.25% TNT levels, females exhibited significantly lower ($p < 0.01$) body weights than controls (Table 60). In the rats that received 0.05% TNT, the apparent depression in body weight was partly due to the group's lower mean body weight compared with controls at the start of the study. Although the females at the 0.25% TNT level also had significantly lower body weights than controls at the start, the much greater difference between high-dose and control means (reflected also in the ratio test, cited A) indicates that, like the males, those females had suppressed growth. The absence of any significant differences in the means for females at the 0.002 and 0.01% TNT levels compared with controls indicates that the treatment did not have a detectable effect on body weights at these levels.

Tables 61 and 62 record the net body weight gains of males and females during the 13-week treatment period. During Week 1, the rats exhibited a significant reduction ($p < 0.01$; cited D in the ratio test) in growth rate as soon as they were put on the 0.25% TNT diet. Presumably, they had a strong aversion to the diet. During Week 2, however, their weight gain improved (B in the ratio test), and no further significant differences were recorded after Week 4 (except for females during Week 11). The weight gain of the males continued to lag noticeably behind that of controls for the remaining 9 weeks of treatment, but the female weight gain did not.

It should be noted that body weight gain tables as presently constructed do not permit a ready comparison of the data when it is desired to learn whether the suppression in body weight is disappearing with time. To see what is meant by this statement, consider the net weight gain during Week 5 for males treated with 0.25% TNT. It was 23.9 g or greater than the control male gain of 21.9 during the same week (Table 61). However, to learn if the high-dose males are growing at a normal rate by Week 5, the comparison should be made with the weight gain of control males of approximately the same mean body weight at the start of the week (Week 3, Table 59). When this is done, then the high-dose males should have grown 37 g, or much more, if their growth rate were now normal. This analysis applies as well to the female data. A better comparison, where the objective is to assess adaptation or recovery, would be to reconstruct these tables in such terms. When interpreting the data in the weight gain tables here and later, this shortcoming must be kept in mind.

Several means at the lower dose level are also cited as being significantly different. In no case, however, was the trend toward consistently low or consistently high values. For example, the net weight gain of males at the 0.002% TNT level increased significantly relative to controls on Week 1 and decreased by approximately the same magnitude on Week 2. Likewise, males at both the 0.002 and 0.01% levels showed a low ($p < 0.05$) net weight gain on Week 7, counteracted partly by a higher net gain on Week 6. These week-to-week variations are to be expected and are not related to treatment.

Further examination of the data in Tables 61 and 62, however, reveals that on Week 9 all male and female groups had unexpectedly low body weight gains, which were offset by correspondingly high body weight gains on Week 10. This observation suggests that a systematic error occurred in the weighings on Week 9 (possibly a different balance was used or the balance used was not tared properly). The compensatory high body weight gains on Week 10 indicate that the weighing procedure used in the first 8 weeks was again being followed. On the last week, females in all groups showed decreases in weight, but these include the weights of animals fasted before sacrifice (half of those remaining in each group).

Tables 63 through 66 present body weights of groups removed from treatment for 4 weeks of recovery. Within 1 or 2 weeks, rats that had been subjected to the 0.25% TNT diet for 4 weeks (Tables 63 and 64) had such a marked recovery of weight that statistical differences between groups were no longer apparent. A similar degree of recovery was observed with high-dose groups exposed to TNT for 13 weeks (Tables 65 and 66), except that a slightly longer time was required. In no case did the absolute means reach control means by the sacrifice date. Therefore, even though the remaining differences are not statistically significant, we cannot conclude that the animals fully recovered.

Tables 67 through 70 present the net weight gain for the groups of rats allowed a 4-week recovery after treatment. The most notable observation was the surge in body weight gain of all high-dose groups during the first week that treatment was terminated ($p < 0.01$). Males on the 0.05% TNT diet also showed increased weight gain during the first week, which was statistically significant ($p < 0.01$) for the 13-week treatment, 4-week recovery groups; this also appears to be a response to removal from treatment. Females both at this level and at the 0.01% TNT level also showed increased food intake the week following removal from treatment that was statistically significant for females treated for 13 weeks.

In summary, TNT had no effect on body weights of male or female rats at the 0.002 and 0.01% levels over the 13 weeks of treatment; however, TNT significantly lowered body weights and weight gain at the 0.25% dose level. A possible dose-related effect on weight gain was detected at the 0.05% TNT level, but it was not as pronounced as at the 0.25% level. Rats allowed a 4-week recovery period substantially recovered from 4 weeks of treatment with TNT at the high dose, but they required a longer recovery period when subjected to 13 weeks of treatment.

Food Consumption

Tables 71 and 72 give the daily food consumption data for control and TNT-treated rats during the 13-week treatment period. The food consumption of both male and female rats given 0.25% TNT was depressed to almost half that of the control rats during the first week, most likely reflecting an aversion to the new diet. The food consumption by these high-dose groups began to improve markedly during the second week as the animals adapted, but it never matched the control rates. Statistical analysis of the data in Tables 11 and 12 indicates that food intake at the highest dose level (0.25%) for males and females was significantly low during almost every week of treatment. Similarly, food consumption for both sexes given 0.05% TNT was slightly lower than that of controls during the first week of treatment and occasionally thereafter. The food intake for all male treatment groups during Week 13 was cited as being significantly low, but this may be due to the unusually high rate of intake for controis during this week. Food intake for males on the 0.002% dose level was also low during Week 8; the reason for this is not known, but it is a singular occurrence and almost certainly cannot be due to the treatment.

The food consumption data in Tables 73 and 74 are expressed in terms of mean body weight. The results parallel those obtained when food consumption was calculated on a per animal basis (Tables 71 and 72) except on Week 9, where female food consumption (g/kg/day) at the 0.25% dose level is slightly higher than that of controls. Statistical analysis of these data again indicates that during the first week, males

and females at the two highest doses consumed their food at significantly lower rates than controls did. Thereafter, only males at the high dose did so with consistency.

Food consumption data for rats that underwent treatment and subsequent recovery appear in Tables 75 through 78. There are no statistical citations during the recovery period and food intake rates are now comparable for all groups. When the data are expressed on a body weight basis (Tables 79 through 82), it is immediately apparent that both sexes at the high dose consumed their food at higher rates than the corresponding control groups did. These rate increases were statistically significant on occasion during the recovery period (Tables 79 and 80). The increases coincide with the earlier observation of a great increase in net body weight gain during the first week of recovery in the high-dose groups.

Tables 83 and 84 present the calculated dose of TNT ingested by the rats at each treatment level during the treatment period.

Organ Weights

Tables 85 and 86 present the organ weights and weight ratios for rats killed after 4 weeks of TNT treatment. In the males given 0.25% TNT (Table 85), spleen weights and weight ratios were significantly high and testes weight and weight ratios were significantly low (both $p < 0.01$). The severity of the changes is reflected in the ratio test on the table, which indicates that the confidence interval for the means is more than 50% different from control means. Livers of high-dose males were also significantly heavier than control livers; the liver weight ratios were significantly elevated but not to the degree of the spleen weight ratios.

Females given the high dose of TNT (Table 86) also had larger spleens than controls ($p < 0.01$, D in the ratio test), and the liver-to-body weight ratio was high ($p < 0.01$, A in the ratio test). Other organ-to-body weight ratios also were high at the 0.25% TNT level (brain-to-body weight significantly so), but not much significance is attached to this because the difference is small and because they probably reflect the low body weights of this group at sacrifice compared with controls.

At the lower treatment levels, occasional deviations from control values were detected. Those that are indicated on the tables as significant are body weight ratios only, but none are abnormal. Microscopic examination of tissues from organs of the animals treated at the 0.05% TNT level did not reveal any lesions that could be attributed to the treatment and thus support any other conclusion.

As Table 87 shows, males sacrificed after 13 weeks of treatment with 0.25 or 0.05% TNT also had enlarged spleens; moreover, the testes of the rats at the 0.25% TNT level were small. All other organ-to-body weight ratios were high and most were significantly so, except for kidneys. Kidney weights, like body weights, were low for this group ($p < 0.05$), and the kidney-to-brain weight and heart-to-brain weight means were also low on the basis of the ratio test (A indicator).

Table 88 indicates that females treated for 13 weeks at the 0.25% level, like the males, had significantly enlarged spleens ($p < 0.01$) and high organ-to-body weight ratios; the kidneys again were an exception, tending to be lower in weight (but not to the same degree as males; no statistical citations). Deviations from control values were occasionally seen in some parameters at the lower dose levels, but none had any apparent toxicological significance. Spleen weights and spleen-to-brain weight ratios at the 0.002% TNT level indicated as being significantly high ($p < 0.05$) were not outside the normal range (see, e.g., other organ weight tables for TNT females to follow).

Tables 89 and 90 present the organ weights and weight ratios for the rats allowed to recover for 4 weeks after 4 weeks of treatment. The testes of males given the high dose remained low relative to control means ($p < 0.05$). However, the C in the ratio test in Table 89, in contrast to the D in Table 85 (4 weeks of continuous treatment with no recovery), indicates that a slight increase in testes size may have occurred. Liver weights and weights of male rats given 0.002, 0.05, and 0.25% TNT were also significantly low, but this probably reflects the somewhat heavier livers of this particular group of control males rather than a toxic effect persisting through the recovery period. Other deviations from control values noted in these recovery groups formed no consistent pattern that could be related definitely to the treatment.

Tables 91 and 92 present the data on organ weights and weight ratios for males and females after 13 weeks of treatment and 4 weeks of recovery. At the 0.25% TNT level, both males and females exhibited a number of deviations from control values. Testicular atrophy was still pronounced among males at this level, to about the same extent as in the males killed at 8 weeks. Kidney weights and kidney-to-brain weight ratios were also significantly low for males at this level (but not for females). Females had notably enlarged livers and spleens. The liver-to-brain weight ratios for these females would also be statistically significant were it not for the high brain weights of these animals. Many organ-to-body weight ratios were high for both sexes that received 0.25% TNT, which resulted from the inability of the animals to recover their body weight completely within the recovery period. Parameters at the lower treatment levels indicated statistically appear to be of no toxicological significance.

In summary, males or females subjected to either 4 or 13 weeks of continuous treatment with 0.25% TNT exhibited enlarged spleens or testicular atrophy. Livers, and possibly kidneys and heart, also appeared to have been affected, but detection of such alterations may depend on the length of treatment, sample size, or sex. When allowed a 4-week recovery period, the high-dose males still exhibited testicular atrophy regardless of the length of the treatment period. For animals treated for 13 weeks, liver and spleen, and possibly kidneys, may have remained different from control values, indicating that a 4-week period may not suffice for recovery in this case.

Hematology*

Tables 93 and 94 show hematological values for rats killed after 4 weeks of treatment with TNT. Although not indicated statistically, a number of parameters at this level were different from control values--the low RBC, Hgb, and Hct and the high MCV in males and females are notable. These data indicate that males and females that received 0.25% TNT in the diet may have experienced a mild anemia. RBC, Hgb, Hct, and MCV values for males at the lower TNT levels were not outside the normal range for rats of this age. The leukocytosis among males at the high-dose level, although not statistically significant, was noteworthy.

Tables 95 and 96 present the hematology data on rats killed after 13 weeks of treatment. The increases in RBC, Hgb, and Hct values in controls over those of rats sacrificed after 4 weeks reflect normal changes expected with maturation of the animals. Among males and females at the 0.25% TNT levels, RBC, Hgb, Hct, and MCHC were low, and MCV, MCH, and WBC were high. Several of these parameters were cited statistically. Moreover, a marked lymphocytosis was apparent at this level. Some parameters, especially the RBC, Hgb, and/or Hct, were significantly lower than control values at the 0.05% TNT level for both sexes and at the 0.01% level for females. As mentioned in the preceding section, the weights were high in males in the 0.05% group but not in the females, and the Hgb and Hct were proportionately lower in the males. These observations may be attributable to increased phagocytosis of hemolyzed erythrocytes in the spleens of males at the 0.05% level that was not detected in the females. This may be a matter of degree related to the particular groups and not to the sex of the animals. Differences in other parameters noted, such as the low WBC of females at the 0.01% TNT level, are most likely due to normal variations from group to group and not to treatment.

* Reticulocytes were not measured in the rat study.

The hematological values for animals after 4 weeks of treatment and 4 weeks of recovery are listed in Tables 97 and 98. The anemia evident at 4 weeks in the high-dose groups was absent. Females at the 0.25% TNT level showed a statistically significant elevation in some of the values (Hgb, Hct, and MCH). These increases were not observed in females at this level after 13 weeks of treatment and 4 weeks of recovery (see below), nor in males at the 8-week sacrifice. These changes may represent some type of overcompensation for the TNT-induced hemolytic anemia that was apparent only in these particular recovery groups.

Tables 99 and 100 record the hematological values of rats after 13 weeks of treatment and 4 weeks of recovery. At the 0.25% TNT level, in addition to Hgb, Hct, and MCH, MCV was elevated significantly and MCHC was decreased significantly in the males. Except for calculated mean corpuscular values, the opposite--if any--trend was observed in females at the 0.25% level. Whereas rats on treatment after 13 weeks had lymphocytosis, the males that continued on study but were allowed 4 weeks of recovery had a slight granulocytosis. High band counts for the female controls is responsible for the citations in the r-test for treatment groups. At the lower TNT levels, no statistically significant changes are noted, although trends are evident in some of the parameters cited above at the 0.05% TNT level, particularly in males (Table C-8).

Clinical Chemistry

Tables 101 and 102 present the clinical chemistry results on rats killed after 4 weeks of treatment. At the high TNT dose, only cholesterol was significantly altered in both sexes. BUN was high and chloride ion concentration was low in males. In females, the electrolyte balance was low, based mainly on changes in Na^+ concentrations, and this was also evident at the 0.01% and 0.05% levels. Total protein due to elevated globulin was high in females, based on the t-test. Several other values (e.g., female creatinine, bilirubin--a sharp increase at the 0.25% level--and SGPT values) were altered in the ratio test, but none of these was considered to be outside the normal range. A/G ratios varied greatly when the treatment groups were contrasted with controls; the same was true of values for LDH, SGOT (in females because of two high control values resulting from hemolyzed samples), and uric acid, contributing in part to citations in the ratio test or uncalculable statistics in this test. Despite the high variability in these test results, the treatment did not appear to have significant effects on these parameters. Thus, at 4 weeks the most prominent and consistent biochemical alteration observed was in cholesterol levels.

Tables 103 and 104 present the clinical chemistry data on the rats killed after 13 weeks. At the high dose of TNT, cholesterol and uric acid were significantly elevated in both sexes, glucose was significantly lower in both sexes, and SGPT was significantly decreased in

males. The cholesterol value for females was clearly outside the normal range (Table B-10); the others were not. SGPT for females at this level was not cited because of the high degree of variance in control values (which also resulted in uncalculable r-tests for treatment groups), but both this mean and that for males are probably low because of the treatment. Glucose was also low in males at the 0.05% level, whereas females that received the 0.002% and 0.01% levels appeared to be affected. Since the variation had no consistent pattern, especially among female groups, and since the values were not outside the normal range for either males or females in our experience (Tables B-9 and B-10), we attributed these results to normal variations due to small group size rather than to the treatment.

Similarly, alkaline phosphatase activity and creatinine levels of males that received the high TNT dose, although significantly different, were not outside the range of other control values in these and the tables that follow. The markedly low iron levels in males at the 0.01, 0.05, and 0.25% TNT levels may have been treatment-related, however. Again, the high variability in the A/G ratio makes interpretation of this ratio difficult for these rats killed after 13 weeks. Several other parameters were indicated in the ratio test at different treatment levels, but the means invariably fell within the normal range (Tables B-9 and B-10).

Tables 105 and 106 give the clinical chemistry data on the rats treated for 4 weeks and allowed to recover for 4 weeks. The only statistically significant finding was the low triglyceride levels of males that were treated at the 0.002, 0.05, and 0.25% TNT levels, but this can be explained by the abnormally high triglyceride mean for control males--obviously an erroneous test result. No parameter indicated statistically was outside the normal range that we have compiled for this species.

The same observation essentially applies to analysis of the data from the 17-week sacrifice, presented in Tables 107 and 108, although the triglyceride level is now much lower for the male controls. (Peninsula Medical did not report uric acid and, at the highest two doses, triglyceride determinations on these samples.) In addition, the A/G ratios and globulin and albumin determinations were inconsistent, a problem we cannot explain. Consequently, we must discount those data. Electrolyte balances in males and females and CO_2 content in females differed significantly from control values at the three highest treatment levels, but the values were not outside the normal ranges.

Cholesterol values at the high dose and SGPT activity were normal in both recovery groups. Thus, the effect of treatment on these parameters was reversible when rats were removed from the TNT regimen.

Histopathology

Tables 109 through 112 summarize the microscopic lesions found in rats treated with TNT for 4 and 13 weeks. Slides of tissues from rats that received the 0.002 and 0.01% TNT levels were prepared but not read because no dose-related responses were apparent at the 0.05% level. After 4 weeks of treatment, all five males at the 0.25% level and one of five males at the 0.05% level had testicular atrophy, and hyperplasia of the interstitial cells was observed in all males at the high dose. All males and females at the 0.25% TNT level had hemosiderosis of the spleen; one of the five females at the 0.05% level also had this lesion. Many rats, male and female, had signs of chronic respiratory disease. Since these signs appeared in the lungs of controls with almost the same frequency as in the lungs of treated rats, we could not unequivocally attribute them to the treatment. In females, the incidence of alveolar collapse and dilation was highest at the 0.25% TNT level and was absent in controls. This observation is common in the rats at other sacrifices. It may be that the treatment, however, is increasing the susceptibility of these animals to disease. Parasites were found in the colons of 3 of 10 rats at the 0.25% TNT level. Although they were found in only one other rat in this study, this finding may also result from the stress of treatment. Hepatomegaly was noted earlier in rats at the 0.25% TNT level; no microscopic lesions associated with this effect were observed.

After 13 weeks of treatment, the most notable findings were hemosiderosis in the spleens of all high-dose males and females and testicular atrophy accompanied by hyperplasia of the interstitial cells and atrophy of the epididymis in all the high-dose males. The incidence of the lesions was greater than in any other group, so these findings are considered to be treatment-related. Because signs of respiratory illness were observed in rats from all groups, this finding is not obviously dose-related. Several other microscopic lesions were found at the 4- and 13-week sacrifices, but by their nature and frequency, they were not attributable to the treatment. However, at the 13-week sacrifices, the appearance of vacuolated cells in the adrenals and of nephrosis in the kidneys of three of five male rats at the 0.05% TNT level was noteworthy.

Tables 113 through 116 summarize the microscopic lesions found in the tissues of rats killed after a 4-week recovery period. After 4 weeks each of treatment and recovery, the only clearly treatment-related findings were testicular atrophy accompanied by hyperplasia of the interstitial cells at the 0.25% TNT level in all five males and hemosiderosis of the spleens in four of the five females. One of five males at that level also had hemosiderosis of the spleen. All the rats at this sacrifice had detectable evidence of chronic respiratory disease. The increased incidence of alveolar dilation noted in the lungs of both males and females as the dose level increased may be treatment-related, but the complications imposed by the presence of respiratory disease in all rats makes this difficult to establish.

At the 0.05% TNT level, three of the five males had regenerative lesions associated with the kidneys, but these lesions did not occur in other groups in a dose-related manner. Other lesions noted in these tissues appeared to be singular and not obviously related to the treatment.

After 13 weeks of treatment and 4 weeks of recovery, rats at both the 0.05 and 0.25% (except for females) TNT levels had an increased incidence of hemosiderosis compared with controls, which may be related to the treatment. The testicular atrophy (accompanied by atrophy of the epididymis in all the males at the highest dose and in one at the next highest dose) was, as in the earlier sacrifices, treatment-related. Occasionally other lesions occurred in tissues from these groups, but their nature and incidence did not suggest that they were treatment-related. A high incidence of chronic respiratory disease among the rats at the sacrifice was again noted.

In summary, the most prevalent microscopic findings that were clearly attributable to the treatment were hemosiderosis of the spleen and testicular atrophy, with accompanying infiltration of the interstitial cells and aplasia of the epididymis. These effects were still apparent in the rats allowed 4 weeks of recovery.

Studies in Mice

Observations

Mice were treated with 0.001, 0.005, 0.025, or 0.125% TNT in the daily diet.

As with the rats, the urine of the mice became red early in the treatment: the color appeared on Day 4 for mice receiving 0.125% TNT and on Day 6 for mice at the 0.025% treatment level. The color disappeared from the urine of all 4-week-treated mice 10 days after discontinuation of treatment and from the urine of the 13-week-treated mice 8 days after termination of treatment. In several groups of males, a high percentage had rough coats and raw skin that developed scabs at various periods during the study due to fighting. A few animals adopted a hunched posture for short times (of no more than a week). No pattern to these symptoms was obvious; males in the control groups were as likely to exhibit them as those in other groups. Apart from the red urine, female groups failed to exhibit similar toxic signs. However, control females and females in the 13-week sacrifice group had rough coats from Weeks 9 through 11 of the study.

Premature deaths in the groups were as follows: one male each at the 0.005, 0.025, and 0.125% TNT levels during Week 2, another from the 0.025% level during Week 6, and one more from the 0.005% level during Week 13. Among females, one control died during Week 8. The

deaths occurred during the nights, so no tissues could be salvaged. For a 90-day study, this attrition rate is not unusual, as indicated by our past experience with mice.

Body Weights

Tables 117 and 118 present the mean body weights of mice treated with TNT for 13 weeks. In males at the 0.025 and 0.125% treatment levels, body weights were lower during the first week (significantly so at the high level, $p < 0.05$) but recovered to levels of control males by the second and third week, respectively. Females receiving 0.025 and 0.125% TNT experienced similar changes in body weight, with recovery complete by Weeks 2 and 6, respectively. As did the rats, the mice exhibited a temporary aversion to the diet at the highest doses (see next section). After 13 weeks of treatment, the body weights of both males and females at these levels still tended to be lower than those of other groups, except as noted below. However, these differences are mainly attributable to the relative differences in the weights of the subpopulations of rats remaining on treatment after Week 4.

The control females had an abnormally low growth pattern during this study. Food intake for these mice was low at the beginning relative to that of other female groups and remained low throughout the study. Possibly an aversion to the food or difficulty in finding their food contributed to the low growth rate, for we could find no reasons for this effect from gross observations of the animals. Comparison of the growth patterns for TNT-treated females and for Swiss-Webster mice used in other subacute studies reveals that, although trends toward lower body weight exist at the highest dose levels, all are within the normal growth range. We consider that 0.125% is the only possible level at which TNT might have had an effect on female body weights, but not a statistically significant one.

Tables 119 and 120 give weight gain per week for the mice treated for 13 weeks. The data confirm the preceding observations and also show that many groups apparently lost weight, most notably during Weeks 9, 12, and 13. Such changes do occur in essentially physically mature mice, and fluctuations of this degree from week to week are to be expected. In contrast to control rats, which doubled or more than tripled in body weight over the 13-week period, the weights of the mice increased by only a factor of 1.5 to 2.0. Correspondingly, less sensitivity was obtained in measuring mouse weights, and week-to-week fluctuation in weight was more apparent in mice than in rats. In addition, fewer r-tests could be performed with the weight gain data on mice compared with mean body weights (Tables 117 and 118), and the statistical indicators in the Bartlett chi-square columns in the weight gain tables were more numerous.

Tables 121 through 128 present the body weights and weight increases of mice treated for 4 or 13 weeks and then allowed to recover for 4 weeks. Corresponding to the conclusions reached above, no surge in the body weight gain of recovery animals occurred during Weeks 5 or 14 at the 0.125% or other level of TNT (Tables 125 and 126). Therefore, if TNT had an effect on mice at this level, it clearly was not pronounced (Tables 121 and 122). The loss in body weight of mice during Weeks 12 and 13 does not represent a deterioration of the health of the animals, since they showed a weight gain on Week 14 or 15; the data reflect the normal weekly variations in body weights of mature mice. Even subgroups of mice within a group (mice of the same group in different cages) grew at fairly different rates--for example, the 8-week (4 of treatment and 4 of recovery) sacrifice males at the 0.001% and 0.005% TNT levels (Table 121) and the full groups (Table 117).

Food Consumption

Tables 129 and 130 give the food intake data on mice that underwent 13 weeks of treatment with TNT. In Week 1, both sexes at the 0.025 and 0.125% TNT levels had lower food consumption rates than did controls. The mice at the 0.025% level had either recovered to or surpassed the normal rate by Week 2 and those at the 0.125% TNT level had resumed normal intake by Week 3. As with the dogs and rats, these effects were attributable to the initial aversion of the mice to the TNT diet. After Week 4, food intake by mice at the 0.025% level was lower because of the smaller size of the animals continuing on treatment. A slightly low intake rate was also observed for females at the highest two dose levels relative to other treatment groups, but the difference was not significant. Control females that grew poorly also ate poorly compared with other female groups.

Food intake data (g/animal/day) for the mice allowed 4 weeks of recovery are in Tables 131 through 134. Without exception, the mice at the 0.125% TNT level slightly increased their food consumption during the first week after removal from treatment. Although none of these changes are cited statistically, it would seem highly coincidental for these increases to have occurred unless they originate from recovery mechanisms. When taken together with the lower body weights of mice at this treatment level, this finding suggests that 0.125% TNT probably continued to suppress body weights after the mice had adjusted to the diet, despite the lack of statistical significance in comparisons of mean body weights or food intake rates.

Food consumption data (g/kg of body weight/day) on mice treated for 13 weeks with or without a 4-week recovery period appear in Tables 135 through 140. No statistically significant differences are cited during the treatment period in any treated group (Tables 135 and 136). Occasionally, citations are recorded in recovery groups (Tables 137 through 140), but the group sizes are too small for the analysis to be meaningful.

Tables 141 and 142 present the dose levels of TNT consumed by the mice weekly during the treatment period.

Organ Weights

Tables 143 and 144 present the organ weights and weight ratios for mice killed after 4 weeks of treatment. Values indicated statistically as altered in males at the 0.001% TNT level were well within the normal range and reflected intergroup variation rather than a toxic response. The heart-to-body weight ratios of the male treatment groups were low because of the high ratio for male controls and not because of treatment. Although females at the 0.001 and 0.005% TNT levels had significantly different brain-to-body weight ratios, no trend was apparent from the data. Similarly, all other values in these tables cited in either the t- or r-tests were likely due to intergroup variations because of the small number of animals in each group. The only treatment-related effect was the enlarged spleens in the males given 0.125% TNT, which resulted in a significantly high spleen-to-body weight ratio.

Table 145 shows that after 13 weeks of TNT treatment, the hearts of males at the 0.001, 0.005, and 0.125% TNT levels were larger than those of controls, leading to significantly greater heart-to-brain ratios in two of those groups. Statistical analysis of the data on females shown in Table 146 revealed a number of changes. Spleen weights at the 0.001 and 0.125% TNT levels were slightly high, but these and all other parameters were within normal ranges for these values (Tables B-11 and B-12). These statistical citations unquestionably arose from the low body weights of the control females in the 13-week sacrifice group. Although a clear dose response is absent for spleen weights at the lower doses, the enlargement in females at the high-dose level may result from the treatment, since this group almost invariably had the largest spleen weights of any at any sacrifice.

Tables 147 and 148 demonstrate that the data on organ weights for males and females after 4 weeks of treatment and 4 of recovery were unremarkable. The high liver weights and liver-to-brain weight ratios for females at the 0.005% TNT level after 4 weeks of treatment with recovery (Table 148) or without recovery (Tables 144) were attributable to the greater body weights of these mice and not to the treatment. Any significantly different liver-to-body or -brain weight ratios in any of the 4-week recovery groups were well within the normal range established in this and other subacute studies with mice.

Tables 149 and 150 show that after 13 weeks of treatment with 0.125% TNT and 4 weeks of recovery, the mice had enlarged spleens and high spleen-to-brain weight ratios; the females also had high spleen-to-body weight ratios. Hemosiderosis of the spleen was observed in these mice (see Histopathology Section), so the enlargement of spleens

was probably treatment-related. In addition, the livers of male mice at the 0.125% TNT level were larger and the liver-to-brain weight ratios were increased significantly, in contrast to these values for mice at the earlier sacrifices. Two of the five mice killed at this level had necrotic tissues in this organ (Histopathology Section). Thus, this effect on livers may also be treatment-related. In analyzing the data on females, the controls for which had low body weights at sacrifice, we emphasized how weights and calculated ratios compared with those of normal female mice or of other treated females to detect any trends that would indicate which parameters, if any, were awry. Therefore, the high liver weight and high liver-to-body weight and spleen-to-brain weight ratios found in female mice at the 0.005% TNT level may not be treatment-related. The liver-to-body and -brain weight ratios for females at the 0.125% TNT level are also not abnormally high.

Hematology

Tables 151 and 152 present the hematology data on mice killed after 4 weeks of treatment with TNT. Whereas statistical tests revealed few significant differences from control values, RBC, Hgb, and Hct were lower and MCV, MCH, and MCHC were increased in mice at the 0.125% TNT level, particularly in the males. The only other notable finding was the increase in % PMN and decrease in % lymphocyte counts in both sexes at this level.

Tables 153 and 154 give the hematology data on mice killed 9 weeks later. These groups showed little evidence of a continuing anemic condition. RBC and Hct for males at the 0.125% TNT level were slightly low, and MCH and MCHC were slightly high but not significantly so. The females at that level showed no anemic pattern. The increase in % PMN and decrease in % lymphocytes were most pronounced for males at the 0.125% level.

Tables 155 and 156 provide the hematology findings on mice treated for 4 weeks and allowed to recover for 4 weeks. Only hematocrits in males at the highest two dose levels were low, but the values were within the normal range (Table B-11). No signs of anemia or of any other abnormality were apparent in treated mice. WBC in females at the 0.125% TNT level was higher than that of other groups, but it was not significantly so.

Tables 157 and 158 show that the findings in mice killed after 13 weeks of treatment and 4 weeks of recovery were equally unremarkable. MCHC in males at the 0.025% TNT level was significantly high but was within normal limits, and PMN and lymphocyte were altered. There was a lack of a clearly defined anemia at the 0.125% TNT level despite the hemosiderosis found in the spleens of these mice (next section).

Histopathology

Tables 159 through 162 summarize the microscopic findings on mice that were treated with TNT for up to 13 weeks with no recovery. After 4 weeks, no treatment-related effects were observed in any groups (tissues from all treated groups were read at this sacrifice); the only possible exception was the detection of hemosiderosis in the spleen of one of five females at the 0.125% TNT level. The incidence of respiratory disease and lesions was less in the mice than in the rats, and their occurrence in the different groups did not indicate that they were treatment-related.

After 13 weeks of treatment, hemosiderosis of the spleen was observed in three of the five males and in all five females at the high dose level, but in no others. This effect was clearly treatment-related. Lung lesions were also more extensive in these groups, but no treatment-related pattern was evident. Other lesions occurred sporadically, particularly at the high dose among females, but their incidence was too infrequent to attribute them unequivocally to the treatment. Paravascular lymphocyte deposits in the kidneys were observed in several mice, including controls, but in a manner that was most likely not related to the treatment.

Tables 163 through 166 summarize the microscopic lesions found in the recovery animals. In the mice killed after 4 weeks of treatment and 4 weeks of recovery (Tables 163 and 164), no lesion occurred with a frequency and distribution among the groups that indicated a relationship to treatment.

In mice killed 4 weeks after the 13-week treatment, several lesions were noted. Hemosiderosis of the spleen in four of the five males and in all five females at the 0.125% TNT level and in one of five males and in four of five females at the 0.025% TNT level was probably related to the treatment. Two control females also exhibited hemosiderosis of the spleen.

The increased incidence of paravascular lymphocytes in the kidneys, livers, and adrenals of treated mice and the slight hemorrhaging evident in the lymph nodes of one of these mice may be treatment-related, but a clear dose relationship was not established. The occurrence of necrosis of the livers in two of five males correlates with the increased liver weights observed in males at the 0.125% TNT level at this sacrifice (Table 149). The effects on the uteri of treated females, although few, may also be treatment-related.

Part 2

DISCUSSION AND CONCLUSIONS

Studies in Dogs

Five male and five female beagles were treated with TNT at 0.20, 2.0, or 20 mg/kg/day by capsule continuously for up to 90 days. One dog of each sex was killed after 4 weeks of treatment and a second male and female were held for 4 weeks of recovery without further treatment. After 13 weeks of treatment, all surviving males and females were killed except for one male and one female, which were held for 4 weeks of recovery.

At 0.20 mg/kg/day, TNT caused no detectable effects on either male or female dogs in any of the parameters measured, and the histopathological examination revealed no abnormalities. We conclude that 0.20 mg of TNT/kg/day is a "no-effect" level.

At the 2.0 mg/kg/day level, a depression of body weight in one of the five females was observed during the 4-week treatment period. The concentration of serum iron was also temporarily lowered in dogs dosed at this level. Both of these effects may be treatment-related (linear trend analysis of serum iron indicates a dose response: Table C-1). In the dogs treated with TNT at 2.0 mg/kg/day for 13 weeks and allowed 4 weeks of recovery, focal lymphocyte deposition in the kidneys was observed in the female, and the male had enlarged kidneys--a condition noted occasionally in dogs not allowed recovery. These observations may also be due to the treatment, but this cannot be established conclusively because a dose relationship was absent (no similar observations in the high-dose male and female) and the observations were made on recovery animals and were absent in animals treated for the same 4-week period. However, recognizing that the responses of a mammalian population to exposure of TNT vary considerably, we believe that these effects at the 2.0 mg/kg/day level are probably related to the treatment.

At the 20-mg/kg/day level, TNT suppressed body weight and food intake temporarily and possibly body weight after prolonged administration. Other effects of treatment noted were increased liver, spleen, and possibly adrenal weights; a mild to moderate normocytic anemia characterized by low RBC, Hgb, Hct, and MCHC and increased MCV; a decrease in PMN (and therefore in the PMN-to-lymphocyte ratio calculated from this); increased cholesterol and bilirubin and decreased SGPT and iron; amber to red urine; and neurological symptoms (primarily inactivity and occasional nystagmus) as the treatment progressed. Other effects that may be treatment-related were the enlarged kidneys and smaller hearts of males after more than 11 weeks of treatment, but these findings included one male that was moribund and was killed early. Nevertheless, the 20-mg/kg/day level of TNT is clearly an effect level.

The condition of three of four dogs placed on recovery after receiving 20 mg TNT per kg daily deteriorated. Their body weights decreased progressively during the recovery period almost up to the time of sacrifice. After 4 weeks of treatment and 4 weeks of recovery, the male dog had leukopenia and was visibly ill. However, it had roundworms in its stools, so whether its illness derived from the parasite or from a delayed toxic

response to TNT is not clear. The female had an enlarged spleen. In the male and female killed at 17 weeks (13 of treatment and 4 of recovery), the body weights had been decreasing, WBC had been increasing, and the anemia (male only) persisted. Some hematological parameters were altered, but in an opposite manner to observations on dogs killed after 13 weeks of treatment, e.g., the high percentage of PMN and low percentage of lymphocytes for both male and female. Lymphocytes seen in the liver of the male may be related to this observation and indicate a reaction of the immune system to TNT or a metabolite. Hemosiderosis was noted in the spleen of the female. Thus, a 4-week recovery period does not appear to be sufficient to completely reverse the toxicity of TNT to dogs; in addition, it is possible that a delayed onset of toxicity carried over into the recovery period for dogs treated at the 20-mg/kg/day level. A 6-month chronic study in dogs is now planned, and it may resolve some of these questions.

Results of past studies on the repeated oral administration of TNT to dogs have been summarized by Dacre and Rosenblatt.[23] The characteristic course of toxicity seems to involve an initial and rapid destruction of RBC in the peripheral circulation (hemolytic type anemia), caused probably by methemoglobinemia and progressing to an aplastic anemia in the more severe cases. RBC, Hgb, and total blood volume were lowered and reticulocytes and anisocytosis appeared. Increased phagocytosis of the hemolyzed cells and breakdown products occurs in spleen, liver, and bone marrow.

The susceptibility of individual dogs to TNT was an important factor.[24] Some dogs given large doses did not show the toxic symptoms of others receiving doses as much as 2 or 4 times smaller.

Other effects were neurological (ataxia, asynergia, marked incoordination, occasional nystagmus). At 100 mg TNT/kg, dogs displayed marked weakness and paresis of the hindquarters and irritation of the gastrointestinal tract (vomiting; salivation; icterus of mucous membranes of the mouth, which developed an ashen or lilac color with time; inflammation in the small intestine, elevated bile levels in the blood and in urine; diarrhea; and dark urine). In a study with females administered 50 mg TNT/kg/day for 12 weeks, 25 premature deaths occurred and inflamed intestines, dark spleens, hemosiderosis in the liver, bone marrow, and lung, and hyperplastic bone marrow were found at sacrifice of those surviving the treatment.[25] Kleiner[26-28] has found evidence of early gastric secretory disorder and an effect on pancreatic enzymes with long-term TNT treatment of dogs. Repeated administration of TNT orally to dogs and monkeys at 1.0 mg/kg daily (or lower) failed to produce toxicological signs in the animals.[29,30]

In this study, we verified several effects reported by these earlier investigators, although we did not observe the same degree of severity, and made several new findings. Among those verified were the early appearance of a pronounced anemia, evidence of adaptation to it as the study progressed, and reversibility--even overcompensation--of the condition when dogs were placed on recovery. Other toxic symptoms were inactivity, occasional nystagmus, decreased iron, increased serum bilirubin, hemosiderosis of the spleen, and liver lesions caused indirectly by the

hemolysis and disruption of the hematopoietic system, and peripheral blood destruction with phagocytosis in these organs. We also observed increased cholesterol in sera, which correlates with the increased level of bile acid reported in an earlier study and resulting from impairment of cholesterol metabolism in the liver.[31,32]

The dog killed ahead of schedule during Week 12 of treatment had evidence of bone marrow hyperplasia and extramedullary hematopoiesis. Considering the high percentage of lymphocytes, low RBC, and related alterations, this dog may have been suffering from an aplastic anemia even in the presence of hyperplasia of the bone marrow. These kinds of effects were reported in earlier studies, but they were more precisely quantitated here as to the dose level producing them.

Some effects that were either not reported earlier or not quantitated sufficiently well were: the temporary depression of body weight and food intake; the enlargement of the liver, spleen, and possibly adrenals; the alterations in blood differentials (decreased PMN cells and increased lymphocytes in treated animals, except for the dog killed early, and the opposite in recovery animals); and the alterations in clinical chemistry (in addition to the above, the decrease in SGPT activity). SGPT apparently was not measured in earlier studies, and it may not have been measured in humans because no effect has been reported. However, SGOT has been found to be elevated in humans after repeated exposure to TNT--in direct contrast to what we observed in the dog.[20,33] Presumably both the increase in SGOT in humans and the decrease in SGPT in dogs stems from an effect of TNT on the same organ, the liver, since in humans liver jaundice is a well known manifestation of TNT toxicity. This difference in the response of these two parameters to TNT requires further investigation. A possible explanation may be that the toxic responses of TNT in the species do not perfectly overlap and that the dog is not completely representative of the manifestations of TNT toxicity in man. A mechanistic interpretation of the effect of TNT on SGPT is offered in the following section.

Studies in Rats

Twenty male and 20 female Sprague-Dawley rats were fed 0.002, 0.010, 0.050, or 0.25% TNT by weight in their diets for up to 90 days. Five rats of each sex from each group were killed at 4 and 13 weeks plus and minus a 4-week recovery period.

At the 0.002% TNT level, the treatment had no detectable effects on any parameter assessed. Histopathological examination of tissues at the 0.05% TNT level failed to reveal any pathological lesions (in contrast to the 0.25% level), so no dose relationship could be established for any lesions observed in tissues from animals at the lower doses, and hence any observed effects could not be treatment-related. Therefore, we conclude that the 0.002% TNT level in the diet constitutes a true "no-effect" level in the rat.

At the 0.01% TNT level, the few findings were almost totally confined to rats treated for longer than 4 weeks. The urine of these rats was red after 50 days, suggesting that the effect of TNT is cumulative. The

red urine indicates the presence of a TNT metabolite and is not necessarily a sign of toxicity. However, after 13 weeks of treatment, blood iron of male rats was significantly low and females evidenced a slight anemia. These observations may be treatment-related, as may be the increase in spleen weights of males at Week 4 (not significantly elevated), since linear trend analysis of the data confirms that a dose relationship to treatment exists (Tables C-7, C-8, and C-9).

At the 0.05% TNT level, some clear toxic symptoms emerged. The body weights and food intake of some sacrifice groups were affected, anemia was evident in 13-week-treated animals, and serum iron of males was low. Spleens were enlarged in the males, and the effect was more pronounced at the 0.25% TNT level; therefore, it is probably dose-related. The hemosiderosis in the spleens in rats of both sexes at the 0.05% TNT level and the increased liver-to-body weight ratios for females that underwent 13 weeks of treatment and 4 weeks of recovery possibly were attributable to the treatment, since there is an obvious dose relationship to these responses. All rats excreted red urine beginning after the first 2 or 3 days of testing.

Rats at the 0.25% TNT level displayed numerous effects. The body weights and food intake were depressed in both sexes, spleens were enlarged (accompanied by hemosiderosis), and testes were atrophied. Livers were larger in 4-week-treated rats, and kidneys were smaller after 13 weeks of treatment (in males and possibly in females). Anemia was increasingly pronounced after 13 weeks, and leukocytosis characterized by lymphocytosis was evident at this time. An elevated uric acid level and decreased SGPT were observed also at 13 weeks, and increased cholesterol was observed at both sacrifices. Changes in bilirubin were significant only in 4-week females.

The anemia, decreased SGPT, lymphocytosis, and a number of other alterations appeared to become more pronounced as the treatment progressed. These observations support the interpretation that the effects of repeated TNT administration are cumulative. Indeed, the depression in SGPT was quite pronounced (almost to the same degree as it was in dogs), and since the effect was only evident after 13 weeks of treatment, we have concluded that it is probably due either to a metabolite of TNT, to binding of TNT to liver proteins or lipids, or to both. The basis for this conclusion is partly the observation that TNT, when added up to 2.0 mM in normal rat sera, failed to have any inhibitory effect on either SGOT or SGPT. Possibly the low SGPT associated with TNT treatment may be derived from selective interference with production of that enzyme in the liver. TNT or metabolites of TNT are known to be inhibitors of protein synthesis.

The effects of short-term exposure to TNT (up to 4 weeks) appear to be almost totally reversible. Body weights of rats at the high dose were still slightly lower (not significantly) than controls and there were lingering signs of overcompensation to the anemia among females at the 0.25% TNT level (also observed after 13 weeks of treatment, but in males). Longer exposure to TNT (13 weeks) requires a longer recovery period for reversibility. Thus, at the 0.05% TNT level, female liver-to-body weight ratios were altered in an apparently dose-related manner. At the 0.25% TNT level, the signs of irreversibility up to 4 weeks were clearer. Body

weights of females remained significantly depressed, they had signs of anemia, and their spleens and livers were enlarged. Testes (particularly) and kidney weights of males were lower than those of controls. The data also indicate the occurrence of slight granulocytosis in the males.

Reports of subacute studies on the effects of TNT on rats in the literature are scarce.[23] Rabbits, rats, and dogs with chronic TNT poisoning reportedly had increased urobilinogen in urine, but no change was observed in serum bilirubin concentration or in osmotic resistance to red blood cells. Rats given TNT orally at 30 mg/kg daily for 6 days exhibited progressively decreased phagocytosis. However, these studies provided virtually no reference for the present work.

Studies in Mice

Mice were treated with 0.001, 0.005, 0.025, or 0.125% TNT in the daily diet for 4 or 13 weeks with or without 4 weeks of recovery. Five of each sex were killed at each sacrifice date.

At the lowest two levels, TNT produced no apparent alterations in any parameter measured. The heart weights and heart-to-brain ratios of the males at 13 weeks are not abnormal for mice this size, nor are spleen weights or spleen-to-brain weight ratios. The spleen weights and spleen-to-brain weight ratio for females at the 0.001% level form no dose relationship with those values for females at higher levels; therefore, the effect at this level cannot be clearly attributed to the treatment. Consequently, we have ascribed the 0.005% TNT diet as the highest "no observable effect" level in this study.

At the 0.025% TNT level, mice showed a temporary decrease in initial body weight, which recovered by the second week. Food intake rates changed in parallel, underlying the changes in body weight. The only other effect clearly attributable to the treatment was the red urine, which appeared in the first week and continued throughout the treatment. Hemosiderosis in the spleens of recovery mice at the 17-week sacrifice may have also been due to the treatment.

At the 0.125% TNT level, several effects were observed. Body weights and food intake were depressed temporarily, and body weights remained depressed over the treatment period. Spleens were affected (enlarged) in some groups with hemosiderosis evident after 13 weeks of the treatment, and heart-to-brain weights were possibly increased. The mice appeared to have mild anemia, at least during the first 4 weeks. Mice at this level frequently exhibited an increase in the PMN-to-lymphocyte ratio without a corresponding change in WBC. All the mice had red urine shortly after starting the treatment; this condition continued until treatment was terminated.

Mice allowed a 4-week recovery did recover if the treatment was restricted to 4 weeks. After longer exposures, mice still had enlarged spleens with hemosiderosis, as well as enlarged livers (with occasional necrosis) and other possibly related effects. However, body weight differences and the anemia were reversed.

No previous subacute studies with TNT in the mouse have been reported.

Interspecies Comparison of Toxicity

The most common observations among the three species were depressed body weight and/or body weight gain and reduced food consumption (temporary with mice), a mild to moderate anemia, and alterations in organ weights, including enlarged spleens (accompanied by hemosiderosis) and livers. In dogs and rats, increased cholesterol (and possibly bilirubin) and decreased SGPT levels were observed. The changes in these two parameters implicate the liver as one of the target organs for TNT toxicity.

The anemia produced by TNT ingestion in these three species is a salient feature and seems to be of the hemolytic type. That is, the anemia is due to extrinsic causes that bring about destruction of the cell after it has matured, as opposed to a faulty hemoglobin or cell synthesis. Usually, the bone marrow was normal to hyperplastic, and some degree of extramedullary hematopoiesis was occasionally evident. The red cells were generally normochronic and normocytic. In one case there was evidence of aplastic anemia (dog A3-39), in which there was not only a reduced number of erythrocytes, but also a reduced number of granulocytes, even in the presence of a hyperplastic bone marrow. This latter observation makes it difficult to speculate on the mechanisms that may be responsible for the anemic condition.

Some findings not common to the three species were testicular atrophy in rats (and possibly dogs), lymphocytosis in rats, accompanied by increased uric acid levels (indicative of increased protein synthesis) and alterations in kidney weights (possibly elevated in dogs, but decreased in rats) and in adrenals (possibly enlarged in dogs). The testicular atrophy is most pronounced in rats and is a common response of that animal to exposure to many chemicals; it requires a high TNT level and is not reversible. No reports on this effect in humans exist at present. The lymphocytosis in rats only may result from differences in metabolic rates in the three species. In addition to the above, the dogs had low serum iron; this is probably related to the observation that the anemia in this species was initially the most severe.

Interspecies comparisons of the relative potency of TNT are difficult to make for two reasons: (1) the doses ingested by one of the test species were not constant with time, and (2) the effective dose levels were not the same in the three species. In the case of the rats, the dose of TNT consumed in their diets was seen to decrease by almost a factor of 2 from Weeks 1 and particularly 2 to near the end of the treatment period, because of the normally lower metabolic activity as the animals approach maturity (Tables 83 and 84). Both dogs and rats showed slight effects at doses approximately the same or lower than the lowest dose at which no effects were observed in mice (Tables 141 and 142), suggesting that these species are more susceptible to the treatment than mice. Symptoms appeared more pronounced in the rat than in mice at all dose levels at which effects of the treatment were noted, affirming this conclusion. Dogs and rats, however, cannot be similarly compared, since

the doses are different at each level. Rats at the highest dose level ingested more TNT than dogs at the highest dose level, which accounts for the more severe and extensive effects seen in the rats.

An interesting note, however, is that SGPT is greatly suppressed in both species at the highest treatment level. In dogs, the effect is observed after 4 weeks--earlier than in rats. In addition, the effect on rats is not observed at the 0.05% level, a level roughly comparable to the high dose administered to dogs. This observation probably reflects differences in the metabolite concentration responsible for depressed SGPT with time in the two species, the dog being slightly more vulnerable as a result.

Water Quality Criteria

One of the main purposes of the present mammalian studies is to generate data that can be used to establish water quality criteria for TNT in water effluents. Sufficient data from human exposure and on the mammalian toxicity of the chemical are not presently available for devising meaningful criteria. For purposes of setting interim standards, the approach proposed by the Environmental Protection Agency for nonstochastic effects may be used.[34] The highest "no observable effect" level for the TNT in the subacute studies is converted into an Acceptable Daily Intake (ADI) figure for man by dividing by an uncertainty factor of 1000, used for situations in which human data, carcinogenic data, or data from long-term feeding studies are unavailable. The ADIs for TNT then are 0.2, 1.42* and 7.76† µg/kg/day from the dog, rat, and mouse data, respectively.

To calculate a maximum recommended concentration of TNT in water bodies, the following equation can be used:

$$C = ADI \times 70/(2 + 0.0187R) \qquad (1)$$

where C is the calculated concentration, 70 is an average body weight for man, R is the bioconcentration factor, 0.0187 is the (assumed) average weight of fish consumed daily (in kg), and 2 is the (assumed) daily water consumption (in liters) for an average adult (70 kg weight).

C can be calculated if R is known. The bioconcentration factor for TNT may be calculated from its estimated oil/water partition coefficient, using structure-activity relationships and the computer

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* From Tables 83 and 84.

† From Tables 141 and 142.

program of Hansch et al.[35] This has been done and a log P has been determined to be 1.7. From the equation of Veith et al.,[36]

$$\log R = 0.76 \log P - 0.23, \qquad (2)$$

R is found to be 11.5. Substitution in Equation (1) yields C values at 6.3, 44.7, and 245 μg/liter (ppb) from the dog, rat, and mouse data, respectively. Thus, there is a nearly 40-fold range among the calculated water concentrations, depending on the species used as a reference.

TABLE 11

EFFECTS OF TNT ON BODY WEIGHTS (KG)
OF MALE DOGS DURING 13 WEEKS OF TREATMENT†

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
INITIAL		9.9 ± .782 (5)	10.2 ± .538 (5)		9.7 ± .320 (5)		10.4 ± .422 (5)	
WEEK 1		9.7 ± .794 (5)	9.7 ± .531 (5)		9.4 ± .319 (5)		9.8 ± .433 (5)	
WEEK 2		10.1 ± .751 (5)	9.9 ± .550 (5)		9.8 ± .312 (5)		9.7 ± .380 (5)	
WEEK 3		10.0 ± .596 (5)	10.1 ± .558 (5)		9.9 ± .350 (5)		9.9 ± .297 (5)	
WEEK 4		10.6 ± .692 (5)	10.7 ± .324 (5)		10.0 ± .329 (5)		10.0 ± .324 (5)	
WEEK 5		10.4 ± .817 (4)	10.7 ± .437 (3)		10.0 ± .606 (3)		10.5 ± .208 (3)	
WEEK 6		[illegible]4 ± .827 (4)	10.6 ± .503 (3)		10.2 ± .635 (3)		10.3 ± .200 (3)	
WEEK 7		10.6 ± .828 (4)	10.6 ± .593 (3)		10.4 ± .753 (3)		10.4 ± .219 (3)	
WEEK 8		10.7 ± .863 (4)	10.7 ± .636 (3)		10.5 ± .666 (3)		10.4 ± .219 (3)	
WEEK 9		11.2 ± 1.05 (3)	10.8 ± .625 (3)		10.6 ± .753 (3)		10.4 ± .233 (3)	
WEEK 10		11.0 ± 1.10 (3)	10.6 ± .617 (3)		10.5 ± .681 (3)		10.1 ± .219 (3)	
WEEK 11		11.1 ± 1.08 (3)	10.6 ± .677 (3)		10.7 ± .681 (3)		10.1 ± .252 (3)	
WEEK 12		11.0 ± 1.06 (3)	10.6 ± .777 (3)		10.6 ± .833 (3)		9.9 ± .285 (3)	
WEEK 13		10.9 ± 1.10 (3)	10.5 ± .736 (3)		10.5 ± .786 (3)		9.9 ± .450 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .
†DATA INCLUDE MALE KILLED DURING WEEK 12.

TABLE 12

EFFECTS OF TNT ON BODY WEIGHTS (KG)
OF FEMALE DOGS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
INITIAL		8.8 ± .250 (5)	8.6 ± .124 (5)		8.9 ± .518 (5)		9.8 ± .390 (5)	
WEEK 1		8.4 ± .215 (5)	8.2 ± .117 (5)		8.4 ± .465 (5)		8.4 ± .434 (5)	
WEEK 2		8.5 ± .211 (5)	8.2 ± .165 (5)		8.6 ± .508 (5)		8.6 ± .495 (5)	
WEEK 3	*	8.5 ± .206 (5)	8.2 ± .124 (5)		8.6 ± .644 (5)		8.6 ± .511 (5)	
WEEK 4		8.9 ± .290 (5)	8.7 ± .172 (5)		8.5 ± .648 (5)		8.8 ± .534 (5)	
WEEK 5		8.4 ± .212 (4)	8.2 ± .153 (3)		9.1 ± 1.01 (3)		8.9 ± .802 (3)	
WEEK 6		8.4 ± .238 (4)	8.4 ± .186 (3)		9.1 ± 1.08 (3)		9.0 ± .821 (3)	
WEEK 7		8.6 ± .218 (4)	8.3 ± .265 (3)		9.1 ± 1.00 (3)		9.2 ± .717 (3)	
WEEK 8		8.6 ± .222 (4)	8.3 ± .233 (3)		9.2 ± 1.14 (3)		9.3 ± .751 (3)	
WEEK 9		8.6 ± .233 (3)	8.3 ± .293 (3)		9.4 ± 1.14 (3)		9.5 ± .717 (3)	
WEEK 10	*	8.4 ± .115 (3)	8.1 ± .153 (3)		9.1 ± 1.10 (3)		9.2 ± .702 (3)	
WEEK 11		8.4 ± .203 (3)	8.2 ± .252 (3)		9.2 ± 1.16 (3)		9.2 ± .736 (3)	
WEEK 12		8.2 ± .086 (3)	8.0 ± .353 (3)		9.1 ± 1.12 (3)		9.0 ± .656 (3)	
WEEK 13	*	8.2 ± .120 (3)	8.1 ± .167 (3)		8.9 ± 1.06 (3)		9.0 ± .656 (3)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - *

TABLE 13

EFFECTS OF TNT ON DIFFERENCES IN BODY WEIGHTS (KG)
OF MALE DOGS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
			TREATMENT GROUPS					
WEEK 1		-.2 ± .086 (5)	-.5 ± .112 (5)		-.4 ± .132 (5)		-.6 ± .196 (5)	
WEEK 2		.3 ± .125 (5)	.2 ± .152 (5)		.4 ± .089 (5)		.0 ± .108 (5)	C
WEEK 3		-.1 ± .172 (5)	.1 ± .189 (5)	•	.2 ± .107 (5)	•	.2 ± .112 (5)	•
WEEK 4	*	.6 ± .223 (5)	.6 ± .296 (5)	•	.1 ± .095 (5)	•	.1 ± .055 (5)	•
WEEK 5		.1 ± .096 (4)	.0 ± .167 (3)	•	.1 ± .176 (3)	•	0.0 ± .153 (3)	•
WEEK 6		.0 ± .025 (4)	-.1 ± .067 (3)	D	.2 ± .033 (3)	D	-.2 ± .058 (3)	D
WEEK 7		.2 ± .048 (4)	.0 ± .133 (3)		.2 ± .133 (3)		.1 ± .033 (3)	
WEEK 8		.1 ± .041 (4)	.0 ± .133 (3)	•	.1 ± .088 (3)	•	0.0 ± .058 (3)	•
WEEK 9		.1 ± .333 (3)	.1 ± .120 (3)	•	.1 ± .088 (3)	•	.1 ± .033 (3)	•
WEEK 10		-.1 ± .088 (3)	-.2 ± .033 (3)	•	-.1 ± .120 (3)	•	-.4 ± .033 (3)	•
WEEK 11		.1 ± .067 (3)	.1 ± .120 (3)	•	.2 ± 0.00 (3)	•	.0 ± .033 (3)	•
WEEK12		-.1 ± .100 (3)	.0 ± .120 (3)	•	-.1 ± .153 (3)	•	-.2 ± .033 (3)	•
WEEK 13		-.1 ± .088 (3)	-.1 ± .145 (3)		-.1 ± .067 (3)	•	-.2 ± .050 (2)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 14

EFFECTS OF TNT ON DIFFERENCES IN BODY WEIGHTS (KG)
OF FEMALE DOGS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T	R	2.0 MG/KG/DAY	T	R	20 MG/KG/DAY	T	R
WEEK 1	*	-.4 ± .037 (5)	-.4 ± .074 (5)		•	-.5 ± .075 (5)		•	-1.4 ± .206 (5)	*	•
WEEK 2		.1 ± .058 (5)	.1 ± .068 (5)		•	.2 ± .107 (5)		•	.2 ± .123 (5)		•
WEEK 3	*	-.1 ± .024 (5)	0.0 ± .071 (5)		•	.0 ± .225 (5)		•	.1 ± .107 (5)		•
WEEK 4		.4 ± .098 (5)	.4 ± .144 (5)			.0 ± .081 (5)	*	D	.2 ± .032 (5)		
WEEK 5		-.3 ± .041 (4)	-.5 ± [illegible] (3)		•	.2 ± .153 (3)		•	.1 ± .067 (3)		•
WEEK 6		0.0 ± .041 (4)	.2 ± .219 (3)		•	.0 ± .120 (3)		•	.1 ± .033 (3)		•
WEEK 7		.2 ± .075 (4)	-.1 ± .058 (3)		B	0.0 ± .100 (3)			.2 ± .115 (3)		
WEEK 8	*	.0 ± .025 (4)	.0 ± [illegible] (3)		•	.1 ± .153 (3)		•	.1 ± .033 (3)	*	•
WEEK 9	+	.0 ± .088 (3)	0.0 ± .058 (3)		•	.2 ± 0.00 (3)		•	.2 ± .067 (3)		•
WEEK 10		-.2 ± .120 (3)	-.2 ± .267 (3)		•	-.3 ± .058 (3)		•	-.3 ± .033 (3)		•
WEEK 11		.0 ± .088 (3)	.1 ± .115 (3)		•	.1 ± .067 (3)		•	.0 ± .120 (3)		•
WEEK12		-.2 ± .115 (3)	-.2 ± .120 (3)		•	-.1 ± .115 (3)		•	-.2 ± .088 (3)		•
WEEK 13		0.0 ± .058 (3)	.0 ± .205 (3)		•	-.2 ± .067 (3)		•	0.0 ± 0.00 (3)		•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 15

EFFECTS OF TNT ON BODY WEIGHTS (KG) OF MALE DOGS
DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
INITIAL	9.9 (5)	11.7 (1)	9.8 (1)	9.1 (1)
WEEK 1	9.7 (5)	11.1 (1)	9.2 (1)	8.9 (1)
WEEK 2	10.1 (5)	11.4 (1)	9.5 (1)	8.8 (1)
WEEK 3	10.0 (5)	11.4 (1)	9.7 (1)	9.0 (1)
WEEK 4	10.6 (5)	11.7 (1)	9.9 (1)	9.1 (1)
WEEK 5	10.4 (4)	11.0 (1)	10.2 (1)	9.2 (1)
WEEK 6	10.4 (4)	11.8 (1)	10.4 (1)	9.1 (1)
WEEK 7	10.6 (4)	11.8 (1)	10.6 (1)	8.5 (1)
WEEK 8	10.7 (4)	11.8 (1)	10.6 (1)	8.4 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES.   TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 16

EFFECTS OF TNT ON BODY WEIGHTS (KG) OF FEMALE DOGS
DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
INITIAL	8.8 (5)	8.2 (1)	8.3 (1)	10.4 (1)
WEEK 1	8.4 (5)	7.9 (1)	7.8 (1)	8.4 (1)
WEEK 2	8.5 (5)	7.9 (1)	7.9 (1)	9.0 (1)
WEEK 3	8.5 (5)	7.9 (1)	7.1 (1)	9.5 (1)
WEEK 4	8.9 (5)	8.2 (1)	6.8 (1)	9.7 (1)
WEEK 5	8.4 (4)	7.9 (1)	7.1 (1)	10.2 (1)
WEEK 6	8.4 (4)	8.0 (1)	7.5 (1)	10.5 (1)
WEEK 7	8.6 (4)	8.0 (1)	7.9 (1)	10.8 (1)
WEEK 8	8.6 (4)	8.1 (1)	8.0 (1)	10.6 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 17

EFFECTS OF TNT ON BODY WEIGHTS (KG) OF MALE DOGS
DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
INITIAL	9.9 (5)	9.9 (1)	9.9 (1)	11.1 (1)
WEEK 1	9.7 (5)	9.3 (1)	10.0 (1)	10.5 (1)
WEEK 2	10.1 (5)	9.5 (1)	10.5 (1)	10.3 (1)
WEEK 3	10.0 (5)	9.8 (1)	11.0 (1)	10.4 (1)
WEEK 4	10.6 (5)	10.1 (1)	11.1 (1)	10.5 (1)
WEEK 5	10.4 (4)	9.8 (1)	11.1 (1)	10.2 (1)
WEEK 6	10.4 (4)	9.6 (1)	11.3 (1)	10.1 (1)
WEEK 7	10.6 (4)	9.5 (1)	11.6 (1)	10.1 (1)
WEEK 8	10.7 (4)	9.4 (1)	11.6 (1)	10.2 (1)
WEEK 9	11.2 (3)	9.6 (1)	11.8 (1)	10.2 (1)
WEEK 10	11.0 (3)	9.4 (1)	11.5 (1)	9.9 (1)
WEEK 11	11.1 (3)	9.3 (1)	11.7 (1)	9.9 (1)
WEEK 12	11.0 (3)	9.1 (1)	11.8 (1)	9.7 (1)
WEEK 13	10.9 (3)	9.0 (1)	11.6 (1)	9.5 (1)
WEEK 14	9.8 (1)	9.0 (1)	11.8 (1)	9.5 (1)
WEEK 15	9.7 (1)	8.9 (1)	11.6 (1)	8.7 (1)
WEEK 16	9.8 (1)	8.9 (1)	11.9 (1)	8.4 (1)
WEEK 17	9.8 (1)	8.8 (1)	12.0 (1)	8.1 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 13

EFFECTS OF TNT ON BODY WEIGHTS (KG) OF FEMALE DOGS
DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS		
		.2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
INITIAL	8.8 (5)	8.8 (1)	10.7 (1)	11.0 (1)
WEEK 1	8.4 (5)	8.5 (1)	10.0 (1)	10.0 (1)
WEEK 2	8.5 (5)	8.8 (1)	10.1 (1)	10.3 (1)
WEEK 3	8.5 (5)	8.6 (1)	10.6 (1)	10.2 (1)
WEEK 4	8.9 (5)	9.0 (1)	10.5 (1)	10.5 (1)
WEEK 5	8.4 (4)	8.0 (1)	11.0 (1)	10.5 (1)
WEEK 6	8.4 (4)	8.6 (1)	11.1 (1)	10.6 (1)
WEEK 7	8.6 (4)	8.7 (1)	11.0 (1)	10.6 (1)
WEEK 8	3.6 (4)	8.7 (1)	11.3 (1)	10.8 (1)
WEEK 9	8.6 (3)	8.7 (1)	11.5 (1)	10.9 (1)
WEEK 10	8.4 (3)	8.4 (1)	11.1 (1)	10.6 (1)
WEEK 11	8.4 (3)	8.7 (1)	11.3 (1)	10.7 (1)
WEEK 12	8.2 (3)	8.7 (1)	11.2 (1)	10.3 (1)
WEEK 13	8.2 (3)	8.4 (1)	10.9 (1)	10.3 (1)
WEEK 14	8.7 (1)	8.5 (1)	10.5 (1)	10.0 (1)
WEEK 15	8.6 (1)	8.5 (1)	10.3 (1)	9.7 (1)
WEEK 16	8.9 (1)	8.7 (1)	10.4 (1)	9.6 (1)
WEEK 17	8.7 (1)	8.8 (1)	10.7 (1)	9.2 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

Table 19

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY) OF MALE DOGS DURING 13 WEEKS OF TREATMENT

Dependent Variable	Control Group	Treatment Groups 0.2 mg/kg/day	2 mg/kg/day	20 mg/kg/day
Week 1	378.4 (5)	322.3 (5)	339.9 (5)	301.9 (5)
Week 2	380.0 (5)	372.4 (5)	386.9 (5)	327.6 (5)
Week 3	385.8 (5)	362.8 (5)	359.7 (5)	339.4 (5)
Week 4	390.8 (5)	338.5 (5)	393.7 (5)	393.1 (5)
Week 5	391.2 (4)	336.5* (4)	400.0* (4)	353.7* (4)
Week 6	400.0 (4)	356.9* (4)	395.7* (4)	367.9* (4)
Week 7	400.0 (4)	356.5* (4)	400.0* (4)	366.3* (4)
Week 8	400.0 (4)	390.7* (4)	400.0* (4)	366.3* (4)
Week 9	384.7 (3)	358.3 (3)	387.0 (3)	343.5 (3)
Week 10	367.2 (3)	345.2 (3)	367.6 (3)	344.3 (3)
Week 11	382.0 (3)	357.8 (3)	385.0 (3)	380.8 (3)
Week 12	399.3 (3)	336.6 (3)	400.0 (3)	328.3 (3)
Week 13	397.0 (3)	369.8 (3)	386.7 (3)	376.6 (2)

Entries are means with group n's in parentheses. TNT was administered daily by capsule.

*Average includes recovery dog.

Table 20

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE DOGS DURING 13 WEEKS OF TREATMENT

Dependent Variable	Control Group	Treatment Groups 0.2 mg/kg/day	2 mg/kg/day	20 mg/kg/day
Week 1	261.6 (5)	233.2 (5)	270.9 (5)	87.2 (5)
Week 2	273.4 (5)	259.9 (5)	307.6 (5)	211.2 (5)
Week 3	269.4 (5)	285.4 (5)	249.6 (5)	249.0 (5)
Week 4	299.6 (5)	278.2 (5)	282.4 (5)	351.1 (5)
Week 5	341.7 (4)	279.0* (4)	355.2* (4)	388.7* (4)
Week 6	332.4 (4)	264.4* (4)	348.7* (4)	373.0* (4)
Week 7	361.0 (4)	281.0* (4)	386.6* (4)	373.3* (4)
Week 8	372.6 (4)	317.3* (4)	390.1* (4)	400.0* (4)
Week 9	352.9 (3)	238.2 (3)	339.0 (3)	317.9 (3)
Week 10	355.3 (3)	260.1 (3)	337.6 (3)	310.0 (3)
Week 11	397.2 (3)	307.6 (3)	369.2 (3)	332.0 (3)
Week 12	400.0 (3)	271.6 (3)	364.5 (3)	272.5 (3)
Week 13	400.0 (3)	317.5 (3)	321.7 (3)	359.8 (3)

Entries are means with group n's in parentheses.

*Average includes recovery dog.

TABLE 21

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE DOGS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS		
		.2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
FINAL WEIGHT (KG)	11.30 (1)	9.90 (1)	10.40 (1)	9.40 (1)
BRAIN	84.00 (1)	76.00 (1)	83.00 (1)	73.00 (1)
HEART	103.00 (1)	98.00 (1)	114.00 (1)	94.00 (1)
KIDNEYS	65.00 (1)	68.00 (1)	67.00 (1)	54.00 (1)
LIVER	400.00 (1)	479.00 (1)	378.00 (1)	405.00 (1)
SPLEEN	31.00 (1)	25.00 (1)	30.00 (1)	55.00 (1)
GONADS	21.00 (1)	21.00 (1)	21.98 (1)	19.00 (1)
ADRENAL	1.65 (1)	1.27 (1)	2.38 (1)	2.13 (1)
THYROID	.90 (1)	.78 (1)	1.22 (1)	.88 (1)
BRAIN/BODY	7.43 (1)	7.68 (1)	7.98 (1)	7.77 (1)
HEART/BODY	9.12 (1)	9.90 (1)	10.96 (1)	10.00 (1)
KIDNEY/BODY	5.75 (1)	6.87 (1)	6.44 (1)	5.74 (1)
LIVER/BODY	35.40 (1)	48.36 (1)	36.35 (1)	43.09 (1)
SPLEEN/BODY	2.74 (1)	2.53 (1)	2.88 (1)	5.85 (1)
GONADS/BODY	1.86 (1)	2.12 (1)	2.11 (1)	2.02 (1)
ADRENAL/BODY	.15 (1)	.13 (1)	.23 (1)	.23 (1)
THYROID/BODY	.08 (1)	.08 (1)	.12 (1)	.09 (1)
HEART/BRAIN	1.23 (1)	1.29 (1)	1.37 (1)	1.29 (1)
KIDNEY/BRAIN	.77 (1)	.89 (1)	.81 (1)	.74 (1)
LIVER/BRAIN	4.76 (1)	6.30 (1)	4.55 (1)	5.55 (1)
SPLEEN/BRAIN	.37 (1)	.33 (1)	.36 (1)	.75 (1)
GONADS/BRAIN	.25 (1)	.28 (1)	.26 (1)	.26 (1)
ADRENAL/BRAIN	.02 (1)	.02 (1)	.03 (1)	.03 (1)
THYROID/BRAIN	.01 (1)	.01 (1)	.01 (1)	.01 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 22

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE DOGS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	TREATMENT GROUPS 2.0 MG/KG/DAY	TREATMENT GROUPS 20 MG/KG/DAY
FINAL WEIGHT (KG)	9.80 (1)	9.10 (1)	9.20 (1)	8.00 (1)
BRAIN	84.00 (1)	72.00 (1)	82.00 (1)	64.00 (1)
HEART	97.00 (1)	109.00 (1)	100.00 (1)	93.00 (1)
KIDNEYS	47.00 (1)	50.00 (1)	44.00 (1)	39.00 (1)
LIVER	376.00 (1)	339.00 (1)	364.00 (1)	497.00 (1)
SPLEEN	54.00 (1)	28.00 (1)	26.00 (1)	41.00 (1)
GONADS	1.15 (1)	1.19 (1)	1.87 (1)	1.82 (1)
ADRENAL	1.89 (1)	1.61 (1)	1.78 (1)	1.30 (1)
THYROID	.91 (1)	1.25 (1)	.81 (1)	.94 (1)
BRAIN/BODY	8.57 (1)	7.91 (1)	8.91 (1)	8.00 (1)
HEART/BODY	9.90 (1)	11.98 (1)	10.87 (1)	11.62 (1)
KIDNEY/BODY	4.80 (1)	5.49 (1)	4.78 (1)	4.88 (1)
LIVER/BODY	38.37 (1)	37.25 (1)	39.57 (1)	62.12 (1)
SPLEEN/BODY	5.51 (1)	3.08 (1)	2.83 (1)	5.13 (1)
GONADS/BODY	.12 (1)	.13 (1)	.20 (1)	.23 (1)
ADRENAL/BODY	.19 (1)	.18 (1)	.19 (1)	.16 (1)
THYROID/BODY	.09 (1)	.14 (1)	.09 (1)	.12 (1)
HEART/BRAIN	1.15 (1)	1.31 (1)	1.22 (1)	1.45 (1)
KIDNEY/BRAIN	.56 (1)	.69 (1)	.54 (1)	.61 (1)
LIVER/BRAIN	4.48 (1)	4.71 (1)	4.44 (1)	7.77 (1)
SPLEEN/BRAIN	.64 (1)	.39 (1)	.32 (1)	.64 (1)
GONADS/BRAIN	.01 (1)	.02 (1)	.02 (1)	.03 (1)
ADRENAL/BRAIN	.02 (1)	.02 (1)	.02 (1)	.02 (1)
THYROID/BRAIN	.01 (1)	.02 (1)	.01 (1)	.01 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 23

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE DOGS DURING 13 WEEKS OF TREATMENT >

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
FINAL WEIGHT (KG)	11.65 (2)	11.20 (2)	10.00 (2)	10.00 (2)
BRAIN	81.20 (2)	86.65 (2)	85.20 (2)	84.60 (2)
HEART	118.50 (2)	107.85 (2)	105.60 (2)	87.80 (2)
KIDNEYS	61.64 (2)	57.88 (2)	53.01 (2)	73.46 (2)
LIVER	486.20 (2)	377.75 (2)	379.65 (2)	601.55 (2)
SPLEEN	47.74 (2)	33.03 (2)	30.20 (2)	73.57 (2)
GONADS	15.58 (2)	21.05 (2)	18.50 (2)	19.38 (2)
ADRENAL	1.80 (2)	2.50 (2)	1.23 (2)	2.67 (2)
THYROID	1.42 (2)	1.73 (2)	1.56 (2)	1.19 (2)
BRAIN/BODY	7.14 (2)	7.74 (2)	8.61 (2)	8.41 (2)
HEART/BODY	10.35 (2)	9.63 (2)	10.70 (2)	8.83 (2)
KIDNEY/BODY	5.41 (2)	5.17 (2)	5.36 (2)	7.37 (2)
LIVER/BODY	41.85 (2)	33.72 (2)	38.64 (2)	60.85 (2)
SPLEEN/BODY	4.07 (2)	2.95 (2)	3.02 (2)	7.47 (2)
GONADS/BODY	1.39 (2)	1.88 (2)	1.86 (2)	1.92 (2)
ADRENAL/BODY	.15 (2)	.22 (2)	.13 (2)	.26 (2)
THYROID/BODY	.12 (2)	.15 (2)	.16 (2)	.12 (2)
HEART/BRAIN	1.47 (2)	1.24 (2)	1.24 (2)	1.05 (2)
KIDNEY/BRAIN	.76 (2)	.67 (2)	.62 (2)	.88 (2)
LIVER/BRAIN	6.08 (2)	4.36 (2)	4.45 (2)	7.18 (2)
SPLEEN/BRAIN	.60 (2)	.38 (2)	.35 (2)	.88 (2)
GONADS/BRAIN	.19 (2)	.24 (2)	.22 (2)	.23 (2)
ADRENAL/BRAIN	.02 (2)	.03 (2)	.01 (2)	.03 (2)
THYROID/BRAIN	.02 (2)	.02 (2)	.02 (2)	.01 (2)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
> A. HIGH DOSE DATA INCLUDES MALE NECROPSIED AT 11 WEEKS

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE DOGS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
FINAL WEIGHT (KG)	8.05 (2)	7.90 (2)	7.90 (2)	8.35 (2)
BRAIN	75.30 (2)	81.70 (2)	84.45 (2)	79.25 (2)
HEART	88.25 (2)	87.30 (2)	117.35 (2)	87.60 (2)
KIDNEYS	46.09 (2)	45.90 (2)	45.97 (2)	48.62 (2)
LIVER	335.70 (2)	285.75 (2)	362.00 (2)	419.35 (2)
SPLEEN	24.58 (2)	22.43 (2)	21.34 (2)	52.48 (2)
GONADS	2.79 (2)	1.34 (2)	2.69 (2)	2.06 (2)
ADRENAL	1.55 (2)	1.56 (2)	1.46 (2)	2.21 (2)
THYROID	1.34 (2)	.96 (2)	1.52 (2)	2.36 (2)
BRAIN/BODY	9.35 (2)	10.34 (2)	10.70 (2)	9.51 (2)
HEART/BODY	10.96 (2)	11.05 (2)	14.60 (2)	10.49 (2)
KIDNEY/BODY	5.72 (2)	5.81 (2)	5.85 (2)	5.83 (2)
LIVER/BODY	41.67 (2)	36.17 (2)	45.62 (2)	50.19 (2)
SPLEEN/BODY	3.05 (2)	2.84 (2)	2.72 (2)	6.32 (2)
GONADS/BODY	.35 (2)	.17 (2)	.34 (2)	.25 (2)
ADRENAL/BODY	.19 (2)	.20 (2)	.18 (2)	.26 (2)
THYROID/BODY	.17 (2)	.12 (2)	.20 (2)	.28 (2)
HEART/BRAIN	1.17 (2)	1.07 (2)	1.37 (2)	1.12 (2)
KIDNEY/BRAIN	.61 (2)	.56 (2)	.55 (2)	.62 (2)
LIVER/BRAIN	4.44 (2)	3.50 (2)	4.27 (2)	5.36 (2)
SPLEEN/BRAIN	.32 (2)	.28 (2)	.25 (2)	.65 (2)
GONADS/BRAIN	.04 (2)	.02 (2)	.03 (2)	.03 (2)
ADRENAL/BRAIN	.02 (2)	.02 (2)	.02 (2)	.03 (2)
THYROID/BRAIN	.02 (2)	.01 (2)	.02 (2)	.03 (2)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 25

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE DOGS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLES	CONTROL GROUP	TREATMENT GROUPS 0.2 MG/KG/DAY	2.0 MG/KG/DAY	20.0 MG/KG/DAY
FINAL WEIGHT (KG)				8.40
BRAIN				87.00
THYROID				.65
HEART				90.00
LIVER				354.00
SPLEEN				22.50
ADRENAL				1.41
KIDNEYS				53.00
TESTES				22.00
BRAIN/BODY WT.				10.36
THYROID/BODY WT.				.08
HEART/BODY WT.				10.71
LIVER/BODY WT.				42.14
SPLEEN/BODY WT.				2.68
ADRENAL/BODY WT.				.17
KIDNEYS/BODY WT.				6.31
TESTES/BODY WT.				2.62
THYROID/BRAIN				.01
HEART/BRAIN				1.03
LIVER/BRAIN				4.07
SPLEEN/BRAIN				.26
ADRENAL/BRAIN				.02
KIDNEYS/BRAIN				.61
TESTES/BRAIN				.25

ONLY HIGH DOSE MALE WAS SACRIFICED.
TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 26

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE DOGS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLES	CONTROL GROUP	TREATMENT GROUPS 0.2 MG/KG/DAY	2.0 MG/KG/DAY	20.0 MG/KG/DAY
FINAL WEIGHT (KG)				10.60
BRAIN				77.00
THYROID				1.11
HEART				100.00
LIVER				359.00
SPLEEN				77.00
ADRENAL				1.39
KIDNEYS				55.00
GONADS				2.89
BRAIN/BODY WT.				7.26
THYROID/BODY WT.				.10
HEART/BODY WT.				9.43
LIVER/BODY WT.				33.87
SPLEEN/BODY WT.				7.26
ADRENAL/BODY WT.				.13
KIDNEYS/BODY WT.				5.19
GONADS/BODY WT.				.27
THYROID/BRAIN				.01
HEART/BRAIN				1.30
LIVER/BRAIN				4.66
SPLEEN/BRAIN				1.00
ADRENAL/BRAIN				.02
KIDNEYS/BRAIN				.71
GONADS/BRAIN				.04

ONLY HIGH DOSE MALE WAS SACRIFICED.
TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 27

EFFECTS OF TNT ON ORGAN WEIGHTS (G), ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G) OF MALE DOGS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
FINAL WEIGHT (KG)	9.80 (1)	8.80 (1)	12.00 (1)	8.10 (1)
BRAIN	77.30 (1)	80.00 (1)	79.00 (1)	84.10 (1)
HEART	113.20 (1)	99.30 (1)	105.50 (1)	120.40 (1)
KIDNEYS	66.12 (1)	57.72 (1)	75.41 (1)	58.21 (1)
LIVER	485.20 (1)	329.60 (1)	410.00 (1)	354.70 (1)
SPLEEN	34.90 (1)	24.92 (1)	33.31 (1)	22.83 (1)
GONADS	14.39 (1)	17.14 (1)	12.61 (1)	15.01 (1)
ADRENAL	1.47 (1)	.46 (1)	1.04 (1)	1.52 (1)
THYROID	.98 (1)	1.34 (1)	.98 (1)	1.24 (1)
BRAIN/BODY	7.89 (1)	9.09 (1)	6.58 (1)	10.38 (1)
HEART/BODY	11.55 (1)	11.28 (1)	8.79 (1)	14.86 (1)
KIDNEY/BODY	6.75 (1)	6.56 (1)	6.28 (1)	7.19 (1)
LIVER/BODY	49.51 (1)	37.45 (1)	34.17 (1)	43.79 (1)
SPLEEN/BODY	3.56 (1)	2.83 (1)	2.78 (1)	2.82 (1)
GONADS/BODY	1.47 (1)	1.95 (1)	1.05 (1)	1.85 (1)
ADRENAL/BODY	.15 (1)	.05 (1)	.09 (1)	.19 (1)
THYROID/BODY	.10 (1)	.15 (1)	.08 (1)	.15 (1)
HEART/BRAIN	1.46 (1)	1.24 (1)	1.34 (1)	1.43 (1)
KIDNEY/BRAIN	.86 (1)	.72 (1)	.95 (1)	.69 (1)
LIVER/BRAIN	6.28 (1)	4.12 (1)	5.19 (1)	4.22 (1)
SPLEEN/BRAIN	.45 (1)	.31 (1)	.42 (1)	.27 (1)
GONADS/BRAIN	.19 (1)	.21 (1)	.16 (1)	.18 (1)
ADRENAL/BRAIN	.02 (1)	.01 (1)	.01 (1)	.02 (1)
THYROID/BRAIN	.01 (1)	.02 (1)	.01 (1)	.01 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 28

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE DOGS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
FINAL WEIGHT (KG)	8.70 (1)	8.80 (1)	10.70 (1)	9.20 (1)
BRAIN	73.40 (1)	81.00 (1)	79.10 (1)	72.90 (1)
HEART	89.00 (1)	85.90 (1)	104.70 (1)	
KIDNEYS	44.26 (1)	43.47 (1)	53.28 (1)	47.99 (1)
LIVER	386.90 (1)	370.60 (1)	385.90 (1)	382.10 (1)
SPLEEN	21.06 (1)	29.53 (1)	31.42 (1)	26.62 (1)
GONADS	1.72 (1)	1.20 (1)	1.38 (1)	1.26 (1)
ADRENAL	1.46 (1)	1.20 (1)	1.51 (1)	1.28 (1)
THYROID	1.02 (1)		1.32 (1)	1.12 (1)
BRAIN/BODY	8.44 (1)	9.20 (1)	7.39 (1)	7.92 (1)
HEART/BODY	10.23 (1)	9.76 (1)	9.74 (1)	
KIDNEY/BODY	5.09 (1)	4.94 (1)	4.98 (1)	5.22 (1)
LIVER/BODY	44.47 (1)	42.11 (1)	36.07 (1)	41.53 (1)
SPLEEN/BODY	2.42 (1)	3.36 (1)	2.94 (1)	2.89 (1)
GONADS/BODY	.20 (1)	.14 (1)	.13 (1)	.14 (1)
ADRENAL/BODY	.17 (1)	.14 (1)	.14 (1)	.14 (1)
THYROID/BODY	.12 (1)		.12 (1)	.12 (1)
HEART/BRAIN	1.21 (1)	1.06 (1)	1.32 (1)	
KIDNEY/BRAIN	.60 (1)	.54 (1)	.67 (1)	.66 (1)
LIVER/BRAIN	5.27 (1)	4.58 (1)	4.88 (1)	5.24 (1)
SPLEEN/BRAIN	.29 (1)	.36 (1)	.40 (1)	.37 (1)
GONADS/BRAIN	.02 (1)	.01 (1)	.02 (1)	.02 (1)
ADRENAL/BRAIN	.02 (1)	.01 (1)	.02 (1)	.02 (1)
THYROID/BRAIN	.01 (1)		.02 (1)	.02 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 29

HEMATOLOGY OF MALE DOGS BEFORE TREATMENT WITH TNT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
RBC (X 10^6)	*	5.99 ± .262 (5)	6.19 ± .100 (5)		5.76 ± .060 (5)		6.07 ± .223 (5)	
HGB (G %)	*	14.65 ± .492 (5)	15.13 ± .101 (5)		13.99 ± .166 (5)		14.76 ± .520 (5)	
HCT (%)	*	41.26 ± 1.57 (5)	42.77 ± .249 (5)		39.85 ± .440 (5)		41.92 ± 1.39 (5)	
MCV $(U)^3$		66.60 ± .678 (5)	67.10 ± .886 (5)		66.90 ± .600 (5)		67.10 ± .400 (5)	
MCH (UUG)		24.46 ± .331 (5)	24.42 ± .313 (5)		24.23 ± .122 (5)		24.30 ± .192 (5)	
MCHC (%)	+	35.35 ± .172 (5)	35.25 ± .184 (5)		31.83 ± 3.19 (5)		35.10 ± .192 (5)	
WBC (X 10^3)		11.45 ± .421 (5)	14.48 ± 1.04 (5)		12.36 ± .933 (5)		14.28 ± .712 (5)	
PMN (%)		32.60 ± 3.40 (5)	39.20 ± 3.62 (5)		31.30 ± 4.39 (5)		40.60 ± 4.29 (5)	
BANDS (%)		22.20 ± 3.53 (5)	20.70 ± 5.09 (5)		24.00 ± 1.31 (5)		25.70 ± 3.52 (5)	
LYMPH (%)		30.30 ± 3.04 (5)	28.90 ± 4.42 (5)		27.90 ± 3.82 (5)		21.60 ± 3.89 (5)	
MONO (%)		5.00 ± .652 (5)	4.70 ± .943 (5)		7.60 ± 1.41 (5)		5.70 ± 1.04 (5)	
EOSIN (%)		10.00 ± 1.92 (5)	6.50 ± 1.01 (5)		9.20 ± 1.85 (5)		6.40 ± 2.62 (5)	
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 30

HEMATOLOGY OF FEMALE DOGS BEFORE TREATMENT WITH TNT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
RBC (X 10^6)		6.52 ± .289 (5)	6.33 ± .306 (5)		6.31 ± .070 (5)		6.27 ± .362 (5)	
HGB (G %)		16.28 ± .721 (5)	16.25 ± .594 (5)		15.55 ± .240 (5)		15.52 ± .949 (5)	
HCT (%)		45.51 ± 1.95 (5)	45.34 ± 1.91 (5)		44.21 ± .527 (5)		43.48 ± 2.40 (5)	
MCV $(U)^3$		67.60 ± .430 (5)	69.40 ± .600 (5)		68.10 ± .245 (5)		67.40 ± .400 (5)	
MCH (UUG)		24.92 ± .209 (5)	25.67 ± .397 (5)		24.61 ± .178 (5)		24.73 ± .280 (5)	
MCHC (%)		35.56 ± .126 (5)	35.68 ± .268 (5)		35.01 ± .248 (5)		35.51 ± .224 (5)	
WBC (X 10^3)		14.64 ± .607 (5)	11.81 ± 1.03 (5)		14.10 ± 1.00 (5)		13.45 ± .901 (5)	
PMN (%)		32.00 ± 5.26 (5)	41.10 ± 3.73 (5)		36.20 ± 1.82 (5)		39.30 ± 2.35 (5)	
BANDS (%)		24.80 ± 2.75 (5)	21.40 ± 3.01 (5)		27.90 ± 4.45 (5)		24.60 ± 2.18 (5)	
LYMPH (%)		31.60 ± 3.96 (5)	29.20 ± 3.15 (5)		24.20 ± 2.61 (5)		25.30 ± 2.37 (5)	
MONO (%)		5.30 ± .875 (5)	4.20 ± .604 (5)		6.10 ± 1.24 (5)		6.20 ± 1.12 (5)	
EOSIN (%)		6.20 ± .903 (5)	4.00 ± 1.14 (5)		5.60 ± .579 (5)		4.10 ± .843 (5)	
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 31

EFFECTS OF TNT ON HEMATOLOGY
OF MALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
RBC (X 10^6)		6.19 ± .221 (5)	6.21 ± .221 (5)		5.87 ± .125 (5)		4.98 ± .164 (5)	
HGB (G %)		14.72 ± .515 (5)	14.82 ± .429 (5)		14.02 ± .315 (5)		12.10 ± .445 (5)	+
HCT (%)		41.56 ± 1.54 (5)	41.80 ± 1.32 (5)		39.88 ± .712 (5)		36.32 ± 1.23 (5)	
MCV $(U)^3$		67.00 ± .548 (5)	67.40 ± .927 (5)		67.60 ± .245 (5)		72.40 ± .812 (5)	
MCH (UUG)		23.88 ± .258 (5)	23.96 ± .308 (5)		23.98 ± .102 (5)		24.40 ± .405 (5)	
MCHC (%)		35.50 ± .152 (5)	35.52 ± .381 (5)		35.30 ± .251 (5)		33.48 ± .191 (5)	+
WBC (X 10^3)		10.74 ± .786 (5)	12.88 ± 1.11 (5)		12.44 ± 1.07 (5)		12.90 ± 1.33 (5)	
PMN (%)		37.80 ± 6.70 (5)	61.60 ± 4.12 (5)	* A	31.60 ± 4.78 (5)		23.40 ± 2.38 (5)	
BANDS (%)		24.40 ± 4.55 (5)	11.80 ± 4.13 (5)		27.40 ± 2.25 (5)		40.40 ± 6.35 (5)	
LYMPH (%)		22.00 ± 2.55 (5)	18.00 ± 4.42 (5)		25.40 ± 3.98 (5)		21.60 ± 2.01 (5)	
MONO (%)		5.60 ± 1.47 (5)	1.60 ± .678 (5)	B	4.40 ± .980 (5)		6.00 ± .447 (5)	
EOSIN (%)		10.20 ± 1.20 (5)	7.00 ± .837 (5)		11.20 ± 2.08 (5)		8.60 ± 2.79 (5)	
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 32

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T	R	2.0 MG/KG/DAY	T	R	20 MG/KG/DAY	T	R
RBC (X 10^6)		6.46 ± .270 (5)	5.96 ± .151 (5)			5.85 ± .238 (5)			4.78 ± .108 (5)		
HGB (G %)		15.70 ± .653 (5)	14.94 ± .303 (5)			14.20 ± .545 (5)			11.76 ± .244 (5)	+	A
HCT (%)		43.84 ± 1.69 (5)	41.78 ± .941 (5)			40.08 ± 1.57 (5)			35.32 ± .871 (5)	+	A
MCV (U)^3		67.80 ± .490 (5)	69.80 ± .663 (5)			68.20 ± .374 (5)			73.40 ± .927 (5)		
MCH (UUG)		24.32 ± .222 (5)	25.10 ± .267 (5)			24.36 ± .218 (5)			24.72 ± .287 (5)		
MCHC (%)		35.86 ± .299 (5)	35.80 ± .134 (5)			35.52 ± .168 (5)			33.46 ± .150 (5)		
WBC (X 10^3)		11.70 ± .470 (5)	12.76 ± 1.27 (5)			11.66 ± 1.13 (5)			12.70 ± 1.19 (5)		
PMN (%)	*	44.40 ± 10.3 (5)	62.20 ± 2.08 (5)			40.60 ± 2.44 (5)			25.40 ± 3.28 (5)		
BANDS (%)	*	23.00 ± 7.67 (5)	9.40 ± 2.01 (5)		A	35.40 ± 2.09 (5)		•	38.40 ± 2.99 (5)		
LYMPH (%)		22.00 ± 1.45 (5)	23.60 ± 1.60 (5)			15.80 ± 2.40 (5)			24.60 ± 3.06 (5)		
MONO (%)	*	4.80 ± 1.88 (5)	1.60 ± .400 (5)		•	3.00 ± .548 (5)		•	5.60 ± 2.04 (5)		•
EOSIN (%)		5.80 ± 1.39 (5)	3.20 ± 1.07 (5)			5.20 ± 1.98 (5)			6.00 ± .447 (5)		
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)			0.00 ± 0.00 (5)			0.00 ± 0.00 (5)		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 33

EFFECTS OF TNT ON HEMATOLOGY
OF MALE DOGS AFTER 8 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
RBC (X 10^6)		6.53 ± .430 (3)	6.58 ± .369 (3)		6.32 ± .244 (3)		5.01 ± .566 (3)	
HGB (G %)		15.30 ± 1.14 (3)	15.23 ± .636 (3)		15.00 ± .473 (3)		1[illegible].10 ± 1.31 (3)	
HCT (%)		43.50 ± 3.14 (3)	44.03 ± 1.93 (3)		42.87 ± 1.14 (3)		36.47 ± 4.14 (3)	
MCV (U)3		66.00 ± 1.15 (3)	66.67 ± 1.20 (3)		67.00 ± 1.00 (3)		71.67 ± 1.20 (3)	
MCH (UUG)		23.17 ± .410 (3)	23.03 ± .484 (3)		23.85 ± .350 (2)		24.03 ± .536 (3)	
MCHC (%)		34.93 ± .033 (3)	34.43 ± 133 (3)		35.00 ± .252 (3)		33.10 ± .379 (3)	+
WBC (X 10^3)		12.13 ± 7.22 (3)	11.90 ± 1.72 (3)		12.33 ± 1.07 (3)		18.17 ± 6.53 (3)	
PMN (%)		26.33 ± 4.70 (3)	43.00 ± 3.21 (3)		36.00 ± 2.00 (3)		25.33 ± 12.7 (3)	
BANDS (%)		38.67 ± 10.7 (3)	20.67 ± 3.93 (3)		26.00 ± 2.65 (3)		31.00 ± 13.9 (3)	
LYMPH (%)	*	28.33 ± 7.86 (3)	23.00 ± 5.13 (3)	•	26.67 ± 1.86 (3)	•	35.00 ± 21.0 (3)	•
MONO (%)	*	0.00 ± 0.00 (3)	4.67 ± 2.33 (3)	•	4.00 ± .577 (3)	* •	6.33 ± 6.33 (3)	•
EOSIN (%)		6.67 ± 2.96 (3)	8.67 ± 2.60 (3)		7.33 ± 3.33 (3)		2.33 ± 1.86 (3)	
BASO (%)		0.00 ± 0.00 (3)	0.00 ± 0.00 (3)		0.00 ± 0.00 (3)		0.00 ± 0.00 (3)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 34

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE DOGS AFTER 6 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.2 MG/KG/DAY	T	R	2.0 MG/KG/DAY	T	R	20 MG/KG/DAY	T	R
			TREATMENT GROUPS								
RBC (X 106)		6.33 ± .128 (3)	6.62 ± .332 (3)			6.06 ± .325 (3)			5.11 ± .062 (3)		
HGB (G %)		14.93 ± .348 (3)	16.07 ± 1.03 (3)			14.20 ± .666 (3)			12.57 ± .338 (3)		
HCT (%)		42.63 ± .876 (3)	45.77 ± 2.67 (3)			41.17 ± 2.17 (3)			37.60 ± .954 (3)		
MCV (U)3		67.00 ± .577 (3)	68.67 ± .667 (3)			67.33 ± .333 (3)			72.67 ± 1.20 (3)		
MCH (UUG)		23.40 ± .231 (3)	24.10 ± .306 (3)			23.27 ± .291 (3)			24.40 ± .379 (3)		
MCHC (%)		34.80 ± .100 (3)	34.93 ± .219 (3)			34.33 ± .291 (3)			33.30 ± .252 (3)	*	
WBC (X 103)		12.73 ± 1.10 (3)	10.30 ± 1.71 (3)			14.03 ± 2.61 (3)			16.47 ± 2.52 (3)		
PMN (%)		32.00 ± 4.04 (3)	50.67 ± 2.03 (3)	*		43.00 ± 2.52 (3)			31.67 ± 5.04 (3)		
BANDS (%)		30.33 ± 6.89 (3)	17.67 ± 3.84 (3)			29.33 ± 4.91 (3)			38.00 ± 1.00 (3)		
LYMPH (%)		29.33 ± 1.86 (3)	24.67 ± 4.26 (3)			20.00 ± 1.15 (3)			23.33 ± 2.73 (3)		
MONO (%)		1.33 ± .667 (3)	3.67 ± 1.86 (3)		•	4.00 ± 2.31 (3)		•	3.33 ± 1.45 (3)		•
EOSIN (%)		7.00 ± 2.08 (3)	3.33 ± 1.20 (3)			4.00 ± 3.00 (3)			3.67 ± 1.33 (3)		
BASO (%)		0.00 ± 0.00 (3)	0.00 ± 0.00 (3)			0.00 ± 0.00 (3)			0.00 ± 0.00 (3)		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 59 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 35

EFFECTS OF TNT ON HEMATOLOGY
OF MALE DOGS AFTER 13 WEEKS OF TREATMENT†

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T	R	2.0 MG/KG/DAY	T	R	20 MG/KG/DAY	T	R
RBC (X 10^6)		6.83 ± .337 (3)	6.83 ± .333 (3)			6.40 ± .302 (3)			5.94 ± .649 (3)		
HGB (G %)		15.57 ± .809 (3)	15.60 ± .473 (3)			14.90 ± .643 (3)			12.90 ± 1.63 (3)		
HCT (%)		45.37 ± 2.45 (3)	45.60 ± 1.12 (3)			43.50 ± 1.78 (3)			36.70 ± 4.88 (3)		
MCV (U)3		66.00 ± 1.15 (3)	66.33 ± 1.45 (3)			67.67 ± .882 (3)			71.67 ± 1.20 (3)		
MCH (UUG)		22.73 ± .410 (3)	22.77 ± .441 (3)			23.23 ± .318 (3)			23.77 ± .521 (3)		
MCHC (%)		34.40 ± .153 (3)	34.17 ± .219 (3)			34.30 ± .100 (3)			32.80 ± .173 (3)	+	
WBC (X 10^3)		9.73 ± .869 (3)	10.70 ± 1.46 (3)			11.67 ± .273 (3)			12.17 ± 2.[illegible] (3)		
PMN (%)		51.00 ± 12.6 (3)	40.00 ± 2.08 (3)			44.00 ± 6.11 (3)			32.67 ± 15.9 (3)		
BANDS (%)		[illegible]2.33 ± 10.3 (3)	23.00 ± 1.73 (3)		•	20.67 ± 6.57 (3)		•	14.33 ± 4.63 (3)		•
LYMPH (%)	*	24.33 ± 3.18 (3)	20.67 ± 1.86 (3)		•	24.00 ± 2.00 (3)		•	46.00 ± 23.[illegible] (3)		
MONO (%)		3.67 ± .333 (3)	7.33 ± 3.48 (3)		•	5.00 ± 1.53 (3)		•	2.67 ± 1.33 (3)		•
EOSIN (%)	*	8.67 ± 5.24 (3)	9.00 ± 0.00 (3)		•	5.33 ± 1.67 (3)		•	4.33 ± 2.33 (3)		•
BASO (%)		0.00 ± 0.00 (3)	0.00 ± 0.00 (3)			0.00 ± 0.00 (3)			0.00 ± 0.00 (3)		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, [illegible] % - D. RATIO TEST CANNOT BE CALCULATED - • .
†DATA INCLUDE MALE [illegible] DURING WEEK 12.

TABLE 36

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE DOGS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.2 MG/KG/DAY	T	R	2.0 MG/KG/DAY	T	R	20 MG/KG/DAY	T	R
			TREATMENT GROUPS								
RBC (X 10⁶)		6.10 ± .180 (3)	6.56 ± .402 (3)			5.99 ± .255 (3)			5.77 ± .360 (3)		
HGB (G %)		14.27 ± .570 (3)	15.93 ± 1.11 (3)			13.80 ± .557 (3)			13.97 ± .939 (3)		
HCT (%)		41.33 ± 1.46 (3)	45.77 ± 2.79 (3)			41.10 ± 1.31 (3)			42.30 ± 3.06 (3)		
MCV (U)3		67.00 ± 0.00 (3)	69.33 ± .667 (3)			68.00 ± 1.15 (3)			72.67 ± .667 (3)		
MCH (UUG)		23.17 ± .145 (3)	24.20 ± .322 (3)			23.00 ± .458 (3)			24.13 ± .120 (3)		
MCHC (%)		34.37 ± .145 (3)	34.77 ± .219 (3)			33.67 ± .353 (3)			33.10 ± .208 (3)	*	
WBC (X 10³)		12.70 ± .721 (3)	9.13 ± 1.07 (3)			11.33 ± .933 (3)			12.40 ± .611 (3)		
PMN (%)		57.67 ± 7.45 (3)	43.00 ± 4.00 (3)			51.67 ± 1.45 (3)			37.33 ± 6.36 (3)		
BANDS (%)		8.00 ± 4.58 (3)	17.00 ± 1.00 (3)		•	19.33 ± 3.18 (3)		•	33.00 ± 4.36 (3)	+	•
LYMPH (%)		21.33 ± 2.85 (3)	26.67 ± 3.28 (3)			19.67 ± 3.53 (3)			22.00 ± 2.08 (3)		
MONO (%)		5.33 ± 1.86 (3)	7.67 ± .882 (3)			4.67 ± 1.76 (3)			2.33 ± .333 (3)		
EOSIN (%)		7.00 ± 3.06 (3)	5.67 ± 1.76 (3)			4.67 ± 2.40 (3)			5.33 ± .667 (3)		
BASO (%)		.67 ± .667 (3)	0.00 ± 0.00 (3)		•	0.00 ± 0.00 (3)		•	0.00 ± 0.00 (3)		•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 37

EFFECTS OF TNT ON HEMATOLOGY
OF MALE DOGS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS		
		.2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
RBC (X 10^6)	6.33 (1)	6.41 (1)	6.63 (1)	6.07 (1)
HGB (G %)	14.90 (1)	15.60 (1)	15.80 (1)	14.20 (1)
HCT (%)	43.20 (1)	44.70 (1)	44.40 (1)	41.00 (1)
MCV $(U)^3$	68.00 (1)	69.00 (1)	67.00 (1)	67.00 (1)
MCH (UUG)	23.40 (1)	24.20 (1)	23.60 (1)	23.20 (1)
MCHC (%)	34.40 (1)	34.80 (1)	35.40 (1)	34.40 (1)
WBC (X 10^3)	13.20 (1)	16.20 (1)	10.70 (1)	6.20 (1)
PMN (%)	34.00 (1)	30.00 (1)	40.00 (1)	41.00 (1)
BANDS (%)	16.00 (1)	27.00 (1)	22.00 (1)	20.00 (1)
LYMPH (%)	34.00 (1)	28.00 (1)	18.00 (1)	35.00 (1)
MONO (%)	2.00 (1)	4.00 (1)	5.00 (1)	1.00 (1)
EOSIN (%)	14.00 (1)	11.00 (1)	15.00 (1)	3.00 (1)
BASO (%)	0.00 (1)	0.00 (1)	0.00 (1)	0.00 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 38

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE DOGS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

		TREATMENT GROUPS		
DEPENDENT VARIABLE	CONTROL GROUP	.2 MG/KG/DAY	2 0 MG/KG/DAY	20 MG/KG/DAY
RBC (X 106)	7.27 (1)	5.25 (1)	6.90 (1)	5.95 (1)
HGB (G %)	17.70 (1)	13.20 (1)	14.20 (1)	14.30 (1)
HCT (%)	50.90 (1)	38.70 (1)	41.30 (1)	41.50 (1)
MCV (U)3	70.00 (1)	73.00 (1)	68.00 (1)	69.00 (1)
MCH (UUG)	24.10 (1)	25.00 (1)	23.50 (1)	23.80 (1)
MCHC (%)	34.60 (1)	33.90 (1)	34.30 (1)	34.80 (1)
WBC (X 103)	15.30 (1)	16.80 (1)	15.80 (1)	16.10 (1)
PMN (%)	43.00 (1)	38.00 (1)	53.00 (1)	21.00 (1)
BANDS (%)	24.00 (1)	16.00 (1)	26.00 (1)	47.00 (1)
LYMPH (%)	25.00 (1)	35.00 (1)	14.00 (1)	28.00 (1)
MONO (%)	4.00 (1)	8.00 (1)	5.00 (1)	3.00 (1)
EOSIN (%)	4.00 (1)	3.00 (1)	2.00 (1)	1.00 (1)
BASO (%)	0.00 (1)	0.00 (1)	0.00 (1)	0.00 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 39

EFFECTS OF TNT ON HEMATOLOGY
OF MALE DOGS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS		
		.2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
RBC (X 10^6)	6.96 (1)	6.14 (1)	6.59 (1)	5.53 (1)
HGB (G %)	16.30 (1)	15.00 (1)	16.20 (1)	17.90 (1)
HCT (%)	46.30 (1)	42.80 (1)	46.30 (1)	37.50 (1)
MCV $(U)^3$	65.00 (1)	68.00 (1)	69.00 (1)	66.00 (1)
MCH (UUG)	23.00 (1)	24.00 (1)	24.10 (1)	22.90 (1)
MCHC (%)	34.80 (1)	34.60 (1)	34.50 (1)	33.90 (1)
WBC (X 10^3)	13.70 (1)	15.00 (1)	12.70 (1)	21.40 (1)
PMN (%)	58.00 (1)	85.00 (1)	57.00 (1)	82.00 (1)
BANDS (%)	2.00 (1)	2.00 (1)	0.00 (1)	1.00 (1)
LYMPH (%)	30.00 (1)	6.00 (1)	24.00 (1)	10.00 (1)
MONO (%)	6.00 (1)	3.00 (1)	7.00 (1)	5.00 (1)
EOSIN (%)	4.00 (1)	4.00 (1)	12.00 (1)	2.00 (1)
BASO (%)	0.00 (1)	0.00 (1)	0.00 (1)	0.00 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES.   TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 40

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE DOGS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
RBC (X 10^6)	6.45 (1)	7.83 (1)	6.37 (1)	6.20 (1)
HGB (G %)	15.40 (1)	19.20 (1)	15.70 (1)	15.10 (1)
HCT (%)	44.20 (1)	54.20 (1)	44.60 (1)	43.90 (1)
MCV $(U)^3$	67.00 (1)	68.00 (1)	69.00 (1)	69.00 (1)
MCH (UUG)	23.40 (1)	24.00 (1)	24.10 (1)	23.90 (1)
MCHC (%)	34.40 (1)	34.90 (1)	34.50 (1)	33.90 (1)
WBC (X 10^3)	11.30 (1)	10.90 (1)	10.10 (1)	21.30 (1)
PMN (%)	54.00 (1)	60.00 (1)	57.00 (1)	89.00 (1)
BANDS (%)	5.00 (1)	0.00 (1)	1.00 (1)	1.00 (1)
LYMPH (%)	27.00 (1)	22.00 (1)	29.00 (1)	9.00 (1)
MONO (%)	9.00 (1)	14.00 (1)	11.00 (1)	5.00 (1)
EOSIN (%)	5.00 (1)	4.00 (1)	2.00 (1)	0.00 (1)
BASO (%)	0.00 (1)	0.00 (1)	0.00 (1)	0.00 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 41

CLINICAL CHEMISTRY OF MALE DOGS BEFORE TREATMENT WITH TNT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS 2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
GLUCOSE (MG %)		107.60 ± 3.45 (5)	117.80 ± 4.44 (5)		97.60 ± 7.99 (5)		105.90 ± 4.52 (5)	
BUN (MG %)		19.60 ± 1.31 (5)	17.40 ± 1.75 (5)		20.50 ± 2.32 (5)		16.60 ± 1.83 (5)	
CREAT (MG %)		.74 ± .029 (5)	.74 ± .043 (5)		.66 ± .033 (5)	A	.72 ± .025 (5)	
URIC ACID (MG)		.31 ± .029 (5)	.36 ± .040 (5)	A	.32 ± .041 (5)		.40 ± .052 (5)	B
NA (MEQ/L)		144.60 ± 1.09 (5)	145.50 ± .548 (5)		143.70 ± 1.83 (5)		145.50 ± 1.70 (5)	
K (MEQ/L)		5.21 ± .053 (5)	4.73 ± .089 (5)	+	4.74 ± .104 (5)	*	4.92 ± .086 (5)	
CO_2 (MEQ/L)		19.30 ± .644 (5)	20.60 ± .941 (5)		20.40 ± .886 (5)		22.10 ± .872 (5)	
CL (MEQ/L)		112.40 ± .367 (5)	111.30 ± .368 (5)		110.80 ± 1.39 (5)		110.30 ± .300 (5)	*
CA (MG %)		10.29 ± .066 (5)	10.35 ± .199 (5)		10.11 ± .175 (5)		10.33 ± .141 (5)	
P (MG %)		5.00 ± .193 (5)	5.08 ± .101 (5)		5.41 ± .296 (5)		4.80 ± .241 (5)	
NA-(CL+CO_2)		12.90 ± 1.20 (5)	13.60 ± .620 (5)		12.50 ± .806 (5)		13.10 ± 1.69 (5)	
CHOL (MG %)		135.10 ± 9.64 (5)	132.70 ± 9.45 (5)		139.30 ± 16.6 (5)		134.90 ± 10.0 (5)	
TRIG (MG %)		26.90 ± 3.72 (5)	26.80 ± 6.09 (5)		38.00 ± 6.58 (5)		35.80 ± 7.61 (5)	
BILI (MG %)		.05 ± 0.00 (5)	.07 ± .012 (5)	C	.10 ± 0.00 (5)	+ D	.10 ± 0.00 (5)	+ D
SGOT (MU/ML)		32.10 ± 1.70 (5)	44.90 ± 2.23 (5)	*	34.50 ± 3.80 (5)		38.70 ± 3.22 (5)	
SGPT (MU/ML)		37.00 ± 3.58 (5)	43.10 ± 3.75 (5)		41.90 ± 7.12 (5)		32.60 ± 2.36 (5)	
LDH (MU/ML)	*	75.40 ± 3.15 (5)	74.10 ± 16.4 (5)		72.10 ± 13.7 (5)		44.10 ± 4.38 (5)	+ B
ALK-P (MU/ML)		97.40 ± 14.4 (5)	133.80 ± 16.2 (5)		186.90 ± 21.2 (5)	*	112.30 ± 21.6 (5)	
IRON (MCG %)		248.70 ± 19.4 (5)	201.30 ± 18.2 (5)		203.60 ± 26.3 (5)		188.80 ± 10.5 (5)	
PROTEIN (GM %)		5.47 ± .064 (5)	5.44 ± .043 (5)		5.42 ± .056 (5)		5.53 ± .102 (5)	
ALBUMIN (GM %)		4.01 ± .029 (5)	3.97 ± .034 (5)		3.88 ± .090 (5)		4.03 ± .089 (5)	
GLOBULIN (GM%)	*	1.46 ± .048 (5)	1.47 ± .020 (5)		1.54 ± .080 (5)		1.50 ± .016 (5)	
A/G RATIO	+	2.84 ± .086 (5)	2.77 ± .025 (5)		2.56 ± .181 (5)		2.69 ± .033 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 42

CLINICAL CHEMISTRY OF FEMALE DOGS BEFORE TREATMENT WITH TNT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T	R	2.0 MG/KG/DAY	T	R	20 MG/KG/DAY	T	R
GLUCOSE (MG %)		103.80 ± 3.39 (5)	115.70 ± 3.20 (5)			110.00 ± 1.78 (5)			114.90 ± 3.26 (5)		
BUN (MG %)		23.80 ± 1.76 (5)	18.70 ± .903 (5)			22.10 ± 2.62 (5)			18.30 ± 1.70 (5)		
CREAT (MG %)		.84 ± .040 (5)	.71 ± .053 (5)		A	.73 ± .020 (5)		A	.78 ± .025 (5)		
URIC ACID (MG)	*	.43 ± .012 (5)	.33 ± .025 (5)	*		.41 ± .033 (5)			.42 ± .083 (5)		
NA (MEQ/L)		146.30 ± .515 (5)	146.60 ± .291 (5)			146.20 ± .644 (5)			145.40 ± .836 (5)		
K (MEQ/L)		4.79 ± .056 (5)	4.66 ± .053 (5)			4.79 ± .075 (5)			4.86 ± .160 (5)		
CO_2 (MEQ/L)		20.10 ± .620 (5)	20.30 ± .515 (5)			21.70 ± .700 (5)			21.70 ± .436 (5)		
CL (MEQ/L)		112.00 ± .612 (5)	111.60 ± .678 (5)			110.90 ± .534 (5)			111.30 ± .625 (5)		
CA (MG %)		10.72 ± .135 (5)	10.59 ± .058 (5)			10.62 ± .156 (5)			10.65 ± .095 (5)		
P (MG %)		5.35 ± .181 (5)	5.13 ± .098 (5)			5.37 ± .245 (5)			5.30 ± .229 (5)		
$NA-(CL+CO_2)$		14.20 ± .538 (5)	14.70 ± .436 (5)			13.60 ± .579 (5)			12.40 ± .967 (5)		
CHOL (MG %)		130.10 ± 11.7 (5)	148.90 ± 10.8 (5)			140.00 ± 10.0 (5)			137.40 ± 2.64 (5)		
TRIG (MG %)		51.00 ± 12.5 (5)	33.00 ± 9.48 (5)			57.40 ± 13.4 (5)			42.70 ± 7.91 (5)		
BILI (MG %)		.09 ± .019 (5)	.10 ± 0.00 (5)		A	.10 ± 0.00 (5)		A	.10 ± 0.00 (5)		A
SGOT (MU/ML)		35.00 ± 1.28 (5)	29.00 ± 3.19 (5)			36.20 ± 3.36 (5)			41.10 ± 3.72 (5)		
SGPT (MU/ML)		32.70 ± 1.36 (5)	24.20 ± 2.61 (5)			33.80 ± 3.27 (5)			29.60 ± 2.35 (5)		
LDH (MU/ML)		75.80 ± 11.9 (5)	50.30 ± 15.9 (5)			52.40 ± 6.13 (5)			61.20 ± 15.9 (5)		
ALK-P (MU/ML)		107.20 ± 15.2 (5)	71.70 ± 7.82 (5)			116.70 ± 16.1 (5)			91.90 ± 9.48 (5)		
IRON (MCG %)		235.80 ± 24.8 (5)	213.70 ± 22.3 (5)			175.10 ± 20.7 (5)			208.70 ± 29.3 (5)		
PROTEIN (GM %)		5.59 ± .066 (5)	5.65 ± .069 (5)			5.57 ± .044 (5)			5.50 ± .089 (5)		
ALBUMIN (GM %)		4.24 ± .097 (5)	4.27 ± .058 (5)			4.18 ± .080 (5)			4.09 ± .094 (5)		
GLOBULIN (GM%)		1.35 ± .059 (5)	1.36 ± .087 (5)			1.39 ± .053 (5)			1.41 ± .068 (5)		
A/G RATIO		3.29 ± .224 (5)	3.29 ± .301 (5)			3.06 ± .172 (5)			2.94 ± .184 (5)		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 43

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF MALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
GLUCOSE (MG %)		102.00 ± 5.76 (5)	107.60 ± 3.03 (5)		105.60 ± 3.33 (5)		95.[illegible]0 ± 2.50 (5)	
BUN (MG %)		14.40 ± .678 (5)	15.80 ± 1.02 (5)		13.72 ± .927 (5)		12.20 ± 1.24 (5)	
CREAT (MG %)		.76 ± .024 (5)	.84 ± .081 (5)		.76 ± .051 (5)		.82 ± .037 (5)	
URIC ACID (MG)	*	.38 ± .020 (5)	.30 ± .045 (5)		.72 ± .020 (5)	+ D	.44 ± .103 (5)	
NA (MEQ/L)		147.20 ± .583 (5)	147.00 ± .707 (5)		146.80 ± .860 (5)		145.00 ± .316 (5)	
K (MEQ/L)		5.18 ± .107 (5)	4.84 ± .093 (5)		4.56 ± .112 (5)	+	5.00 ± .084 (5)	
CO_2 (MEQ/L)		22.80 ± .490 (5)	23.40 ± .872 (5)		24.20 ± .490 (5)		23.20 ± .374 (5)	
CL (MEQ/L)		111.40 ± .510 (5)	110.40 ± .678 (5)		110.80 ± .490 (5)		111.00 ± .548 (5)	
CA (MG %)		10.48 ± .168 (5)	10.36 ± .231 (5)		10.38 ± .174 (5)		10.42 ± .102 (5)	
P (MG %)		4.16 ± .133 (5)	4.70 ± .302 (5)		4.32 ± .199 (5)		4.56 ± .194 (5)	
NA-(CL+CO_2)		13.00 ± .548 (5)	13.20 ± .374 (5)		11.80 ± .583 (5)		10.80 ± .583 (5)	
CHOL (MG %)		131.20 ± 11.6 (5)	129.60 ± 7.65 (5)		135.80 ± 10.9 (5)		181.20 ± 10.5 (5)	*
TRIG (MG %)		31.40 ± 5.46 (5)	20.20 ± 3.28 (5)		18.60 ± 1.81 (5)	A	31.20 ± 2.40 (5)	
BILI (MG %)		.10 ± 0.00 (5)	.12 ± .020 (5)	A	.12 ± .020 (5)	A	.16 ± .024 (5)	D
SGOT (MU/ML)		39.80 ± 2.35 (5)	43.60 ± 2.94 (5)		43.40 ± 3.61 (5)		44.20 ± 4.37 (5)	
SGPT (MU/ML)		36.00 ± 3.51 (5)	34.60 ± 2.94 (5)		29.80 ± 4.07 (5)		13.60 ± 3.60 (5)	+ C
LDH (MU/ML)		79.20 ± 17.1 (5)	87.60 ± 13.9 (5)		101.80 ± 31.2 (5)		85.00 ± 9.41 (5)	
ALK-P (MU/ML)	*	95.00 ± 13.2 (5)	148.20 ± 42.3 (5)		166.80 ± 14.6 (5)	*	113.40 ± 14.1 (5)	
IRON (MCG %)		273.20 ± 8.22 (5)	256.40 ± 20.4 (5)		144.40 ± 20.3 (5)	+ B	172.80 ± 27.6 (5)	* A
PROTEIN (GM %)		5.82 ± .124 (5)	5.72 ± .097 (5)		5.66 ± .075 (5)		5.88 ± .086 (5)	
ALBUMIN (GM %)		4.46 ± .098 (5)	4.38 ± .097 (5)		4.28 ± .074 (5)		4.30 ± 0.00 (5)	
GLOBULIN (GM%)		1.36 ± .060 (5)	1.34 ± .103 (5)		1.38 ± .074 (5)		1.58 ± .086 (5)	
A/G RATIO		3.30 ± .152 (5)	3.36 ± .277 (5)		3.14 ± .227 (5)		2.76 ± .160 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 44

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF FEMALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
GLUCOSE (MG %)		110.00 ± 4.39 (5)	108.60 ± 2.87 (5)		101.40 ± 3.71 (5)		101.80 ± 1.77 (5)	
BUN (MG %)		15.00 ± .316 (5)	14.00 ± 1.14 (5)		13.70 ± 1.04 (5)		12.20 ± .916 (5)	
CREAT (MG %)		.74 ± .060 (5)	.66 ± .093 (5)		.76 ± .024 (5)		.78 ± .037 (5)	
URIC ACID (MG)	*	.28 ± .037 (5)	.20 ± .032 (5)		.74 ± .024 (5)	+ D	.42 ± .102 (5)	
NA (MEQ/L)		147.00 ± .949 (5)	147.60 ± .510 (5)		146.60 ± .245 (5)		145.40 ± .600 (5)	
K (MEQ/L)		4.76 ± .169 (5)	4.72 ± .136 (5)		4.68 ± .058 (5)		4.98 ± .124 (5)	
CO_2 (MEQ/L)		23.20 ± .490 (5)	22.60 ± .400 (5)		23.20 ± .374 (5)		22.40 ± .510 (5)	
CL (MEQ/L)		110.20 ± .374 (5)	111.00 ± .775 (5)		112.20 ± .374 (5)		110.80 ± .374 (5)	
CA (MG %)		10.46 ± .129 (5)	10.66 ± .150 (5)		10.50 ± .230 (5)		10.32 ± .139 (5)	
P (MG %)		3.68 ± .146 (5)	4.32 ± .345 (5)		3.76 ± .112 (5)		4.26 ± .112 (5)	
NA-(CL+CO_2)		13.60 ± .678 (5)	14.00 ± .316 (5)		11.20 ± .374 (5)		12.20 ± .800 (5)	
CHOL (MG %)		133.00 ± 13.2 (5)	184.00 ± 14.0 (5)		183.20 ± 11.1 (5)		208.20 ± 13.8 (5)	+ A
TRIG (MG %)		35.20 ± 7.14 (5)	37.20 ± 4.72 (5)		24.20 ± 1.93 (5)		48.60 ± 8.99 (5)	
BILI (MG %)		.10 ± 0.00 (5)	.12 ± .020 (5)	A	.12 ± .020 (5)	A	.18 ± .020 (5)	* D
SGOT (MU/ML)		36.00 ± 1.18 (5)	38.00 ± 1.76 (5)		45.00 ± 4.16 (5)		40.00 ± 3.61 (5)	
SGPT (MU/ML)	*	32.20 ± 2.91 (5)	18.80 ± 2.01 (5)	* A	31.60 ± 7.29 (5)		8.60 ± 1.91 (5)	+ D
LDH (MU/ML)	+	45.40 ± 1.75 (5)	75.40 ± 25.4 (5)		71.60 ± 7.15 (5)	* A	82.00 ± 16.0 (5)	
ALK-P (MU/ML)		118.60 ± 14.5 (5)	82.20 ± 8.01 (5)		138.40 ± 22.0 (5)		140.60 ± 22.5 (5)	
IRON (MCG %)		226.20 ± 14.9 (5)	246.80 ± 10.7 (5)		161.40 ± 9.57 (5)	A	171.20 ± 23.3 (5)	
PROTEIN (GM %)		5.90 ± .114 (5)	6.00 ± .063 (5)		5.80 ± .127 (5)		5.98 ± .162 (5)	
ALBUMIN (GM %)		4.52 ± .086 (5)	4.72 ± .074 (5)		4.52 ± .086 (5)		4.34 ± .051 (5)	
GLOBULIN (GM%)	*	1.38 ± .037 (5)	1.28 ± .058 (5)		1.28 ± .066 (5)		1.64 ± .181 (5)	
A/G RATIO		3.28 ± .058 (5)	3.72 ± .208 (5)		3.54 ± .157 (5)		2.78 ± .301 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 45

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF MALE DOGS AFTER 8 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
GLUCOSE (MG %)		103.67 ± 8.09 (3)	112.00 ± 1.15 (3)		115.33 ± 2.60 (3)		99.33 ± 6.98 (3)	
BUN (MG %)		15.00 ± 1.00 (3)	14.33 ± 1.20 (3)		13.33 ± .882 (3)		10.27 ± .636 (3)	* A
CREAT (MG %)		1.10 ± .058 (3)	1.07 ± .088 (3)		1.07 ± .133 (3)		.60 ± .058 (3)	* B
URIC ACID (MG)		.53 ± .067 (3)	.57 ± .088 (3)		.53 ± .067 (3)		.37 ± .033 (3)	
NA (MEQ/L)		144.67 ± 1.33 (3)	141.67 ± .882 (3)		144.67 ± .882 (3)		141.67 ± 2.40 (3)	
K (MEQ/L)		4.87 ± .088 (3)	4.60 ± .100 (3)		4.40 ± .115 (3)		4.50 ± .153 (3)	
CO_2 (MEQ/L)		20.67 ± .882 (3)	21.33 ± .333 (3)		21.00 ± 0.00 (3)		19.00 ± 1.00 (3)	
CL (MEQ/L)		112.67 ± .333 (3)	109.67 ± 1.86 (3)		112.33 ± 1.33 (3)		110.33 ± 1.86 (3)	
CA (MG %)		10.53 ± .338 (3)	10.23 ± .219 (3)		10.37 ± .088 (3)		10.37 ± .410 (3)	
P (MG %)	*	3.83 ± .088 (3)	4.03 ± .233 (3)		4.43 ± .033 (3)	*	3.73 ± .517 (3)	
NA-(CL+CO_2)		11.33 ± .667 (3)	10.67 ± 1.20 (3)		11.33 ± .882 (3)		12.67 ± .882 (3)	
CHOL (MG %)		147.00 ± 11.2 (3)	126.00 ± 8.96 (3)		144.00 ± 20.1 (3)		208.33 ± 33.6 (3)	
TRIG (MG %)		25.33 ± 3.48 (3)	21.33 ± 5.36 (3)		24.00 ± 5.03 (3)		28.67 ± 5.78 (3)	
BILI (MG %)		.10 ± 0.00 (3)	.13 ± .033 (3)	B	.10 ± 0.00 (3)		.20 ± 0.00 (3)	* D
SGOT (MU/ML)		36.00 ± 3.06 (3)	40.67 ± 1.33 (3)		36.67 ± 2.67 (3)		44.00 ± 3.06 (3)	
SGPT (MU/ML)		35.00 ± 5.57 (3)	41.33 ± 1.33 (3)		30.67 ± .882 (3)		15.00 ± 5.57 (3)	* B
LDH (MU/ML)		52.67 ± 15.4 (3)	68.00 ± 15.7 (3)		42.00 ± 2.08 (3)		95.67 ± 11.3 (3)	
ALK-P (MU/ML)		66.33 ± 13.3 (3)	92.00 ± 17.6 (3)		140.00 ± 20.2 (3)		148.33 ± 38.1 (3)	
IRON (MCG %)		200.00 ± 9.07 (3)	195.00 ± 20.6 (3)		179.33 ± 14.9 (3)		136.00 ± 69.8 (3)	
PROTEIN (GM %)		6.07 ± .088 (3)	5.67 ± .088 (3)		5.97 ± .167 (3)		6.13 ± .033 (3)	
ALBUMIN (GM %)		4.77 ± .167 (3)	4.50 ± .153 (3)		4.67 ± .145 (3)		4.23 ± .120 (3)	
GLOBULIN (GM%)		1.30 ± .115 (3)	1.17 ± .067 (3)		1.30 ± .208 (3)		1.90 ± .153 (3)	
A/G RATIO		3.73 ± .448 (3)	3.90 ± .351 (3)		3.80 ± .802 (3)		2.27 ± .240 (3)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 46

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF FEMALE DOGS AFTER 8 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
GLUCOSE (MG %)		94.33 ± 6.06 (3)	109.33 ± 7.97 (3)		108.67 ± 3.48 (3)		104.00 ± 4.36 (3)	
BUN (MG %)		14.33 ± .882 (3)	12.20 ± 1.40 (3)		13.67 ± 1.20 (3)		13.00 ± .577 (3)	
CREAT (MG %)		1.10 ± 0.00 (3)	.70 ± .058 (3)	+ C	.67 ± .033 (3)	+ C	.70 ± .058 (3)	+ C
URIC ACID (MG)		.60 ± .058 (3)	.40 ± 0.00 (3)	B	.30 ± .058 (3)	+ D	.33 ± .033 (3)	* C
NA (MEQ/L)		140.00 ± 1.53 (3)	141.67 ± 2.33 (3)		144.67 ± .882 (3)		142.67 ± 1.45 (3)	
K (MEQ/L)		4.17 ± .219 (3)	4.40 ± .231 (3)		4.63 ± .033 (3)		4.53 ± .285 (3)	
CO_2 (MEQ/L)		19.33 ± .333 (3)	20.00 ± .577 (3)		20.33 ± .882 (3)		20.00 ± .577 (3)	
CL (MEQ/L)		111.00 ± 1.73 (3)	108.00 ± 2.08 (3)		111.33 ± .882 (3)		110.00 ± 1.53 (3)	
CA (MG %)		10.13 ± .273 (3)	10.73 ± .318 (3)		10.37 ± .120 (3)		10.37 ± .167 (3)	
P (MG %)		3.60 ± .404 (3)	4.07 ± .751 (3)		3.90 ± .404 (3)		4.00 ± .208 (3)	
NA-(CL+CO_2)		9.67 ± .882 (3)	13.67 ± .882 (3)	* A	13.00 ± .577 (3)		12.67 ± .333 (3)	
CHOL (MG %)		129.67 ± 19.2 (3)	166.00 ± 23.8 (3)		183.67 ± 8.09 (3)		235.33 ± 38.6 (3)	
TRIG (MG %)		23.00 ± 2.08 (3)	18.33 ± 4.91 (3)		23.00 ± 2.52 (3)		23.67 ± 6.39 (3)	
BILI (MG %)		.13 ± .033 (3)	.13 ± .033 (3)		.17 ± .033 (3)	B	.23 ± .033 (3)	D
SGOT (MU/ML)		35.67 ± 1.33 (3)	33.67 ± 2.60 (3)		42.67 ± 2.91 (3)		36.00 ± 2.08 (3)	
SGPT (MU/ML)		34.33 ± 3.84 (3)	21.67 ± 2.03 (3)	* A	22.67 ± 1.33 (3)	* A	4.00 ± 1.15 (3)	+ D
LDH (MU/ML)		33.33 ± 2.33 (3)	34.67 ± 3.53 (3)		53.57 ± 8.25 (3)		46.67 ± 17.8 (3)	
ALK-P (MU/ML)		138.33 ± 26.9 (3)	60.67 ± 8.51 (3)		144.67 ± 42.7 (3)		153.67 ± 30.7 (3)	
IRON (MCG %)		200.33 ± 13.3 (3)	277.33 ± 78.7 (3)		263.00 ± 45.0 (3)		153.67 ± 22.3 (3)	
PROTEIN (GM %)		5.77 ± .219 (3)	5.80 ± .153 (3)		5.83 ± .067 (3)		5.83 ± .120 (3)	
ALBUMIN (GM %)		4.63 ± .058 (3)	4.67 ± .176 (3)		4.67 ± .088 (3)		4.30 ± .058 (3)	
GLOBULIN (GM%)		1.13 ± .133 (3)	1.23 ± .133 (3)		1.17 ± .033 (3)		1.53 ± .145 (3)	
A/G RATIO		4.17 ± .384 (3)	3.90 ± .513 (3)		4.03 ± .186 (3)		2.83 ± .291 (3)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - # .

TABLE 47

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF MALE DOGS AFTER 13 WEEKS OF TREATMENT[†]

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
GLUCOSE (MG %)		104.67 ± 2.96 (3)	112.33 ± 3.38 (3)		114.33 ± 2.85 (3)		97.67 ± 11.3 (3)	
BUN (MG %)		16.00 ± 2.00 (3)	15.33 ± 1.20 (3)		14.33 ± .882 (3)		10.33 ± .882 (3)	A
CREAT (MG %)		.73 ± .033 (3)	.77 ± .068 (3)		.77 ± .033 (3)		.60 ± .058 (3)	
URIC ACID (MG)		.37 ± .033 (3)	.40 ± 0.00 (3)		.37 ± .033 (3)		.30 ± .058 (3)	A
NA (MEQ/L)		146.33 ± .333 (3)	146.33 ± .333 (3)		147.67 ± .667 (3)		144.00 ± 1.53 (3)	
K (MEQ/L)		4.83 ± .186 (3)	4.53 ± .145 (3)		4.57 ± .133 (3)		4.67 ± .186 (3)	
CO_2 (MEQ/L)		21.67 ± .882 (3)	22.67 ± .667 (3)		22.33 ± .333 (3)		20.67 ± 1.76 (3)	
CL (MEQ/L)		111.00 ± .577 (3)	109.67 ± .882 (3)		110.67 ± .333 (3)		110.33 ± 1.45 (3)	
CA (MG %)		11.20 ± .231 (3)	10.80 ± .306 (3)		10.73 ± .133 (3)		10.70 ± 0.00 (3)	
P (MG %)		3.77 ± .033 (3)	3.90 ± .208 (3)		3.67 ± .353 (3)		3.90 ± .173 (3)	
$NA-(CL+CO_2)$		13.67 ± .333 (3)	14.00 ± .577 (3)		14.67 ± .333 (3)		13.00 ± 0.00 (3)	
CHOL (MG %)	*	129.67 ± 8.99 (3)	115.33 ± 9.53 (3)		127.33 ± 24.1 (3)		134.67 ± 66.8 (3)	
TRIG (MG %)	+	17.67 ± .882 (3)	10.67 ± .333 (3)	*	10.00 ± 1.73 (3)	*	31.67 ± 17.6 (3)	
BILI (MG %)		.13 ± .033 (3)	.13 ± .033 (3)		.17 ± .033 (3)	B	.23 ± .033 (3)	D
SGOT (MU/ML)		40.00 ± 2.65 (3)	43.67 ± 1.86 (3)		48.33 ± 3.38 (3)		43.33 ± 10.1 (3)	
SGPT (MU/ML)		34.33 ± 5.17 (3)	43.00 ± 4.36 (3)		37.67 ± 3.28 (3)		14.00 ± 6.35 (3)	B
LDH (MU/KL)		54.33 ± 13.0 (3)	64.33 ± 10.7 (3)		54.33 ± 9.17 (3)		69.33 ± 3.18 (3)	
ALK-P (MU/ML)		94.67 ± 19.3 (3)	123.00 ± 26.7 (3)		179.67 ± 22.8 (3)		150.67 ± 27.5 (3)	
IRON (MCG %)		262.00 ± 15.9 (3)	205.67 ± 14.2 (3)		215.00 ± 18.3 (3)		231.67 ± 66.7 (3)	
PROTEIN (GM %)		5.90 ± 0.00 (3)	5.57 ± .033 (3)		5.60 ± .058 (3)		6.17 ± .418 (3)	
ALBUMIN (GM %)		4.67 ± .120 (3)	4.53 ± .067 (3)		4.53 ± .088 (3)		3.97 ± .186 (3)	*
GLOBULIN (GM%)	*	1.23 ± .120 (3)	1.07 ± .088 (3)	•	1.07 ± .145 (3)	•	2.20 ± .600 (3)	
A/G RATIO		3.87 ± .524 (3)	4.30 ± .416 (3)		4.47 ± .745 (3)		2.10 ± .500 (3)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .
[†]DATA INCLUDE MALE KILLED DURING WEEK 12.

TABLE 48

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF FEMALE DOGS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.2 MG/KG/DAY	T R	2.0 MG/KG/DAY	T R	20 MG/KG/DAY	T R
			TREATMENT GROUPS					
GLUCOSE (MG %)		111.00 ± 6.25 (3)	103.67 ± 6.94 (3)		109.67 ± 2.40 (3)		105.33 ± 4.26 (3)	
BUN (MG %)	*	15.00 ± .577 (3)	13.67 ± .333 (3)		14.50 ± 2.18 (3)		12.67 ± .333 (3)	*
CREAT (MG %)		.57 ± .033 (3)	.77 ± .033 (3)	+ C	.70 ± 0.00 (3)	* B	.70 ± 0.00 (3)	* B
URIC ACID (MG)		.37 ± .067 (3)	.40 ± .058 (3)		.30 ± 0.00 (3)	A	.37 ± .033 (3)	
NA (MEQ/L)		144.00 ± 1.00 (3)	148.33 ± 1.45 (3)		144.33 ± 2.19 (3)		146.67 ± .882 (3)	
K (MEQ/L)		4.53 ± .176 (3)	4.70 ± .252 (3)		4.77 ± .067 (3)		4.83 ± .120 (3)	
CO_2 (MEQ/L)		20.67 ± 1.86 (3)	21.33 ± .333 (3)		22.33 ± .882 (3)		20.67 ± .667 (3)	
CL (MEQ/L)		110.67 ± .882 (3)	110.00 ± 1.15 (3)		108.00 ± 1.15 (3)		111.00 ± .577 (3)	
CA (MG %)		10.43 ± .088 (3)	10.90 ± .115 (3)		10.50 ± .289 (3)		10.33 ± .176 (3)	
P (MG %)		3.57 ± .176 (3)	3.67 ± .433 (3)		3.77 ± .267 (3)		4.07 ± .328 (3)	
NA-(CL+CO_2)		12.67 ± 1.86 (3)	17.00 ± 1.15 (3)		14.00 ± .577 (3)		15.00 ± .577 (3)	
CHOL (MG %)		155.00 ± 18.6 (3)	133.00 ± 9.61 (3)		161.67 ± 15.8 (3)		167.00 ± 13.6 (3)	
TRIG (MG %)		30.67 ± 11.2 (3)	10.00 ± 3.21 (3)	A	12.00 ± 2.31 (3)	A	15.00 ± 2.31 (3)	
BILI (MG %)		.13 ± .033 (3)	.13 ± .033 (3)		.20 ± 0.00 (3)	D	.30 ± 0.00 (3)	+ D
SGOT (MU/ML)		38.67 ± 5.04 (3)	41.33 ± .882 (3)		49.00 ± 4.04 (3)		45.67 ± .882 (3)	
SGPT (MU/ML)		32.00 ± 5.13 (3)	28.00 ± 2.65 (3)		27.33 ± 2.33 (3)		7.67 ± 1.20 (3)	+ D
LDH (MU/ML)		81.33 ± 30.6 (3)	49.00 ± 16.2 (3)		44.67 ± 2.19 (3)		68.00 ± 13.9 (3)	
ALK-P (MU/ML)		178.00 ± 68.0 (2)	94.67 ± 14.4 (3)		192.33 ± 53.5 (3)		155.00 ± 18.9 (3)	
IRON (MCG %)		254.67 ± 11.9 (3)	218.00 ± 12.1 (3)		215.33 ± 7.31 (3)		194.33 ± 36.6 (3)	
PROTEIN (GM %)		5.90 ± .058 (3)	5.83 ± .088 (3)		5.60 ± .058 (3)		5.70 ± .200 (3)	
ALBUMIN (GM %)		4.53 ± .033 (3)	4.87 ± .120 (3)		4.43 ± .088 (3)		4.53 ± .133 (3)	
GLOBULIN (GM%)		1.37 ± .033 (3)	.97 ± .176 (3)	A	1.17 ± .033 (3)		1.17 ± .067 (3)	
A/G RATIO	*	3.33 ± .088 (3)	5.40 ± 1.07 (3)		3.83 ± .186 (3)		3.90 ± .100 (3)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   TNT ADMINISTERED DAILY BY CAPSULE.
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 49

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF MALE DOGS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
GLUCOSE (MG %)	86.00 (1)	117.00 (1)	107.00 (1)	117.00 (1)
BUN (MG %)	14.00 (1)	12.00 (1)	17.00 (1)	21.00 (1)
CREAT (MG %)	.90 (1)	.80 (1)	.80 (1)	1.10 (1)
URIC ACID (MG)	.30 (1)	.10 (1)	.20 (1)	.60 (1)
NA (MEQ/L)	142.00 (1)	140.00 (1)	138.00 (1)	143.00 (1)
K (MEQ/L)	4.90 (1)	4.80 (1)	4.50 (1)	5.10 (1)
CO_2 (MEQ/L)	22.00 (1)	19.00 (1)	21.00 (1)	18.00 (1)
CL (MEQ/L)	113.00 (1)	113.00 (1)	109.00 (1)	112.00 (1)
CA (MG %)	10.80 (1)	10.60 (1)	9.90 (1)	9.70 (1)
P (MG %)	4.30 (1)	4.50 (1)	3.80 (1)	4.60 (1)
NA-(CL+CO_2)	7.00 (1)	8.00 (1)	8.00 (1)	13.00 (1)
CHOL (MG %)	113.00 (1)	134.00 (1)	124.00 (1)	177.00 (1)
TRIG (MG %)	28.00 (1)	15.00 (1)	13.00 (1)	24.00 (1)
BILI (MG %)	.10 (1)	.10 (1)	.10 (1)	.10 (1)
SGOT (MU/ML)	37.00 (1)	39.00 (1)	35.00 (1)	42.00 (1)
SGPT (MU/ML)	33.00 (1)	32.00 (1)	41.00 (1)	28.00 (1)
LDH (MU/ML)	24.00 (1)	111.00 (1)	44.00 (1)	52.00 (1)
ALK-P (MU/ML)	87.00 (1)	92.00 (1)	122.00 (1)	102.00 (1)
IRON (MCG %)	165.00 (1)	135.00 (1)	148.00 (1)	308.00 (1)
PROTEIN (GM %)	5.60 (1)	5.70 (1)	5.40 (1)	5.70 (1)
ALBUMIN (GM %)	4.40 (1)	4.50 (1)	4.00 (1)	4.50 (1)
GLOBULIN (GM%)	1.20 (1)	1.20 (1)	1.40 (1)	1.20 (1)
A/G RATIO	3.60 (1)	3.80 (1)	2.90 (1)	3.80 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 50

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF FEMALE DOGS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
GLUCOSE (MG %)	1[illegible]5.00 (1)	120.00 (1)	113.00 (1)	97.00 (1)
BUN (MG %)	15.00 (1)	17.00 (1)	12.00 (1)	13.00 (1)
CREAT (MG %)	.80 (1)	.80 (1)	.60 (1)	1.00 (1)
URIC ACID (MG)	.20 (1)	.30 (1)	.60 (1)	.60 (1)
NA (MEQ/L)	141.00 (1)	140.00 (1)	144.00 (1)	145.00 (1)
K (MEQ/L)	4.10 (1)	4.90 (1)	4.30 (1)	5.00 (1)
CO_2 (MEQ/L)	20.00 (1)	23.00 (1)	20.[illegible] (1)	22.00 (1)
CL (MEQ/L)	110.00 (1)	110.00 (1)	112.00 (1)	112.00 (1)
CA (MG %)	11.00 (1)	10.50 (1)	9.70 (1)	10.40 (1)
P (MG %)	3.40 (1)	3.70 (1)	3.80 (1)	4.10 (1)
NA-(CL+CO_2)	11.00 (1)	7.00 (1)	12.00 (1)	11.00 (1)
CHOL (MG %)	186.00 (1)	242.00 (1)	136.00 (1)	170.00 (1)
TRIG (MG %)	130.00 (1)	19.00 (1)	16.00 (1)	30.00 (1)
BILI (MG %)	0.00 (1)	.10 (1)	.10 (1)	.20 (1)
SGOT (MU/ML)	37.00 (1)	31.00 (1)	35.00 (1)	39.00 (1)
SGPT (MU/ML)	18.00 (1)	23.00 (1)	26.00 (1)	30.00 (1)
LDH (MU/ML)	75.00 (1)	39.00 (1)	34.00 (1)	92.00 (1)
ALK-P (MU/ML)	155.00 (1)	113.00 (1)	161.00 (1)	59.00 (1)
IRON (MCG %)	189.00 (1)	192.00 (1)	192.00 (1)	258.00 (1)
PROTEIN (GM %)	6.40 (1)	5.70 (1)	5.60 (1)	6.00 (1)
ALBUMIN (GM %)	4.90 (1)	4.50 (1)	4.40 (1)	4.60 (1)
GLOBULIN (GM%)	1.50 (1)	1.20 (1)	1.20 (1)	1.40 (1)
A/G RATIO	3.30 (1)	3.80 (1)	3.70 (1)	3.30 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES.   TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 51

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF MALE DOGS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
GLUCOSE (MG %)	112.00 (1)	108.00 (1)	110.00 (1)	96.00 (1)
BUN (MG %)	16.00 (1)	17.00 (1)	15.00 (1)	17.00 (1)
CREAT (MG %)	.60 (1)	.50 (1)	.70 (1)	.60 (1)
URIC ACID (MG)	.50 (1)	.50 (1)	.40 (1)	.40 (1)
NA (MEQ/L)	141.00 (1)	143.00 (1)	146.00 (1)	148.00 (1)
K (MEQ/L)	[illegible].50 (1)	4.80 (1)	4.60 (1)	[illegible].40 (1)
CO_2 (MEQ/L)	22.00 (1)	22.00 (1)	25.00 (1)	24.00 (1)
CL (MEQ/L)	109.00 (1)	113.00 (1)	112.00 (1)	112.00 (1)
CA (MG %)	9.70 (1)	9.60 (1)	10.40 (1)	10.90 (1)
P (MG %)	4.00 (1)	4.30 (1)	4.50 (1)	4.00 (1)
NA-(CL+CO_2)	10.00 (1)	8.00 (1)	9.00 (1)	12.00 (1)
CHOL (MG %)	118.00 (1)	99.00 (1)	122.00 (1)	146.00 (1)
TRIG (MG %)	25.00 (1)	13.00 (1)	18.00 (1)	23.00 (1)
BILI (MG %)	.10 (1)	.10 (1)	.10 (1)	.10 (1)
SGOT (MU/ML)	37.00 (1)	37.00 (1)	30.00 (1)	27.00 (1)
SGPT (MU/ML)	60.00 (1)	44.00 (1)	33.00 (1)	22.00 (1)
LDH (MU/ML)	35.00 (1)	70.00 (1)	35.00 (1)	54.00 (1)
ALK-P (MU/ML)	105.00 (1)	90.00 (1)	90.00 (1)	115.00 (1)
IRON (MCG %)	236.00 (1)	257.00 (1)	257.00 (1)	287.00 (1)
PROTEIN (GM %)	5.70 (1)	5.40 (1)	5.50 (1)	5.80 (1)
ALBUMIN (GM %)	4.60 (1)	4.20 (1)	4.70 (1)	5.00 (1)
GLOBULIN (GM%)	1.10 (1)	1.20 (1)	.90 (1)	.80 (1)
A/G RATIO	4.20 (1)	3.50 (1)	5.90 (1)	6.30 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. TNT ADMINISTERED DAILY BY CAPSULE.

TABLE 52

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF FEMALE DOGS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS		
		.2 MG/KG/DAY	2.0 MG/KG/DAY	20 MG/KG/DAY
GLUCOSE (MG %)	120.00 (1)	100.00 (1)	108.00 (1)	121.00 (1)
BUN (MG %)	14.00 (1)	20.00 (1)	10.00 (1)	13.00 (1)
CREAT (MG %)	.50 (1)	.50 (1)	.50 (1)	.70 (1)
URIC ACID (MG)	.50 (1)	.40 (1)	.40 (1)	.40 (1)
NA (MEQ/L)	143.00 (1)	141.00 (1)	146.00 (1)	144.00 (1)
K (MEQ/L)	4.80 (1)	4.70 (1)	4.00 (1)	4.40 (1)
CO_2 (MEQ/L)	23.00 (1)	26.00 (1)	29.00 (1)	21.00 (1)
CL (MEQ/L)	111.00 (1)	111.00 (1)	108.00 (1)	112.00 (1)
CA (MG %)	10.00 (1)	9.20 (1)	10.00 (1)	10.20 (1)
P (MG %)	3.90 (1)	3.30 (1)	3.80 (1)	3.50 (1)
NA-(CL+CO_2)	9.00 (1)	4.00 (1)	7.00 (1)	11.00 (1)
CHOL (MG %)	170.00 (1)	115.00 (1)	127.00 (1)	170.00 (1)
TRIG (MG %)	53.00 (1)	18.00 (1)	23.00 (1)	24.00 (1)
BILI (MG %)	.10 (1)	.10 (1)	.10 (1)	.10 (1)
SGOT (MU/ML)	29.00 (1)	45.00 (1)	31.00 (1)	31.00 (1)
SGPT (MU/ML)	22.00 (1)	57.00 (1)	40.00 (1)	30.00 (1)
LDH (MU/ML)	35.00 (1)	57.00 (1)	37.00 (1)	46.00 (1)
ALK-P (MU/ML)	110.00 (1)	80.00 (1)	70.00 (1)	160.00 (1)
IRON (MCG %)	265.00 (1)	280.00 (1)	207.00 (1)	262.00 (1)
PROTEIN (GM %)	5.80 (1)	4.90 (1)	5.40 (1)	5.70 (1)
ALBUMIN (GM %)	4.50 (1)	3.50 (1)	4.50 (1)	4.70 (1)
GLOBULIN (GM%)	1.30 (1)	1.40 (1)	.90 (1)	1.00 (1)
A/G RATIO	3.50 (1)	2.50 (1)	5.00 (1)	4.70 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES.   TNT ADMINISTERED DAILY BY CAPSULE.

Table 53

MICROSCOPIC LESIONS IN MALE AND FEMALE DOGS AFTER 4 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.2	2	20	
	Group Designation				
	A0	A1	A2	A3	
	Animal Number				
Male					
Lung					
Alveolar collapse and dilation				31	
Female					
Brain					
Lymphocytic cutting in thalamus	02				
Pituitary					
Occasional cysts			22		
Spleen					
Pigmentation (hemosiderosis)				32	
Thymus					
Hyperplasia			22		

Table 54

MICROSCOPIC LESIONS IN MALE DOGS AFTER 13 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.2	2	20*	
	Group Designation				
	A0	A1	A2	A3	
	Animal Number				
Adrenal					
Vacuolated cortical cells	09	13	29	33	
Bone marrow					
Hyperplasia				39	
Colon					
Hemorrhage in mucosa		19			
Duodenum					
Nematode parasite in lumen				39	
Kidney					
Congestion	03/09	13		33	
Liver					
Extramedullary hematopoiesis				39	
Parenchymal pigmented macrophages				33	
Lung					
Alveolar collapse	09	13		33,39	
Alveolar collapse and dilation	03	19	23/29		
Lung worm focus	09				
Parathyroid					
One or several cysts		13			
Pituitary					
Occasional cysts		19			
Prostate					
Hyperplasia				39	
Testes					
Atrophy	03			39	
Interstitial cell hyperplasia	03				

* Dog A3-39 was killed during the 12th week of treatment on day 79.

Table 55

MICROSCOPIC LESIONS IN FEMALE DOGS AFTER 13 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.2	2	20	
	Group Designation				
	A0	A1	A2	A3	
	Animal Number				
Adrenal					
Vacuolated cortical cells	10	20		34	
Kidney					
Congestion	10		30		
Liver					
Granulomas		20			
Solitary focus of triaditis			30		
Parenchymal pigmented microphages				36	
Lung					
Alveolar collapse	04	1	24	34/40	
Alveolar collapse and dilation	10	20			
Strands of parenchymal lymphocytes	04				
Parathyroid					
One or several cysts			30		
Spleen					
Pigmentation (hemosiderosis)		14			

Table 56

MICROSCOPIC LESIONS IN MALE AND FEMALE DOGS AFTER 4 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.2	2	20	
	Group Designation				
	A0	A1	A2	A3	
	Animal Number				
Male					
Kidney					
Slight focal nephrocalcinosis				37	
Female					
Kidney					
Slight focal nephrocalcinosis				38	
Spleen					
Congestion				38	

Table 57

MICROSCOPIC LESIONS IN MALE DOGS AFTER 13 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.2	2	20	
	Group Designation				
	A0	A1	A2	A3	
	Animal Number				
Jejunum					
Chronic enteritis		15			
Liver					
Parenchymal lymphocytes				35	
Lung					
Alveolar collapse and dilation	05	15	25	35	
Pituitary					
Occasional cysts		15			

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MICROSCOPIC LESIONS IN FEMALE DOGS AFTER 13 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.2	2	20	
	Group Designation				
	A0	A1	A2	A3	
	Animal Number				
Kidney					
Interstitial lymphocytes			26		
Lung					
Alveolar collapse and dilation	06		26	36	
Alveolar histiocytosis				36	
Pituitary					
Occasional cysts	06	16			
Spleen					
Pigmentation (hemosiderosis)				36	
Vagina					
Vaginitis				36	

TABLE 59

EFFECTS OF [illegible] ON BODY WEIGHTS (G)
OF MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
INITIAL		168.2 ± 1.67 (20)	165.4 ± 1.95 (20)		167.7 ± 1.85 (20)		168.6 ± 2.17 (20)		169.9 ± 1.82 (20)	
WEEK 1	*	215.3 ± 2.32 (20)	220.4 ± 2.38 (20)		210.5 ± 4.51 (20)		212.1 ± 3.53 (20)		181.6 ± 3.68 (20)	+ A
WEEK 2		269.0 ± 3.10 (20)	269.5 ± 3.18 (20)		261.1 ± 3.58 (20)		261.0 ± 4.10 (20)		216.9 ± 5.14 (20)	+ A
WEEK 3		306.1 ± 3.58 (20)	307.7 ± 3.84 (20)		300.4 ± 3.18 (20)		293.2 ± 3.97 (20)		252.8 ± 4.90 (20)	+ A
WEEK 4		342.1 ± 5.22 (20)	345.6 ± 4.36 (20)		337.7 ± 3.84 (20)		330.3 ± 4.33 (20)		279.9 ± 4.62 (20)	+ A
WEEK 5		371.1 ± 6.24 (15)	358.4 ± 5.98 (10)		360.8 ± 5.93 (10)		355.0 ± 8.04 (10)		294.5 ± 7.59 (10)	+ A
WEEK 6		389.7 ± 7.49 (15)	378.8 ± 6.73 (10)		383.8 ± 7.06 (10)		376.7 ± 8.52 (10)		302.3 ± 8.03 (10)	+ A
WEEK 7		411.9 ± 8.52 (15)	394.3 ± 6.89 (10)		399.5 ± 7.21 (10)		395.8 ± 9.43 (10)		318.4 ± 8.30 (10)	+ A
WEEK 8		432.9 ± 9.66 (15)	414.6 ± 7.72 (10)		420.0 ± 7.56 (10)		415.2 ± 9.70 (10)		333.6 ± 7.46 (10)	+ A
WEEK 9		451.7 ± 13.0 (10)	410.3 ± 8.54 (10)		415.7 ± 8.62 (10)		419.9 ± 8.19 (10)		342.7 ± 9.02 (10)	+ A
WEEK 10		468.4 ± 13.0 (10)	435.7 ± 9.31 (10)		448.5 ± 7.57 (10)		443.6 ± 8.99 (10)		353.7 ± 8.79 (10)	+ A
WEEK 11		477.9 ± 13.0 (10)	443.7 ± 9.64 (10)		459.3 ± 7.84 (10)		451.9 ± 9.75 (10)		363.2 ± 9.86 (10)	+ A
WEEK 12		492.9 ± 13.3 (10)	451.7 ± 10.6 (10)		468.2 ± 7.09 (10)		460.5 ± 10.4 (10)		371.0 ± 9.29 (10)	+ A
WEEK 13		499.5 ± 14.7 (10)	459.2 ± 10.9 (10)		473.8 ± 9.22 (10)		465.8 ± 12.3 (10)		369.0 ± 9.52 (10)	+ B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 60

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
INITIAL		158.1 ± 1.49 (20)	151.7 ± 1.48 (20)		153.1 ± 1.42 (20)		148.2 ± 1.76 (20)	+	146.9 ± 1.53 (20)	+
WEEK 1		175.1 ± 1.69 (20)	172.6 ± 2.20 (20)		175.2 ± 2.10 (20)		168.8 ± 2.09 (20)		146.8 ± 2.00 (20)	+ A
WEEK 2		196.3 ± 1.80 (20)	188.1 ± 2.92 (20)		192.8 ± 2.41 (20)		182.6 ± 2.71 (20)	+	161.0 ± 2.46 (20)	+ A
WEEK 3		207.6 ± 1.81 (20)	197.9 ± 2.96 (20)		205.8 ± 2.73 (20)		192.9 ± 2.54 (20)	+	173.1 ± 2.66 (20)	+ A
WEEK 4	*	218.6 ± 1.85 (20)	214.9 ± 3.68 (20)		217.4 ± 3.49 (20)		204.4 ± 3.22 (20)	+	181.4 ± 2.79 (20)	+ A
WEEK 5		223.5 ± 2.61 (15)	222.4 ± 5.45 (10)		228.0 ± 6.16 (10)		211.3 ± 3.88 (10)		190.2 ± 4.63 (10)	+
WEEK 6		236.7 ± 4.28 (15)	229.9 ± 5.28 (10)		244.1 ± 7.88 (10)		214.5 ± 4.15 (10)		192.2 ± 4.56 (10)	+ A
WEEK 7		238.3 ± 2.77 (15)	238.1 ± 5.91 (10)		247.4 ± 7.65 (10)		221.0 ± 3.92 (10)		197.4 ± 5.12 (10)	+ A
WEEK 8		246.3 ± 3.09 (15)	246.6 ± 6.38 (10)		252.1 ± 7.51 (10)		230.7 ± 4.74 (10)		201.7 ± 5.78 (10)	+ A
WEEK 9		248.7 ± 4.74 (10)	240.4 ± 6.00 (10)		248.6 ± 7.30 (10)		229.3 ± 3.91 (10)		204.5 ± 5.19 (10)	+ A
WEEK 10		254.6 ± 3.85 (10)	255.6 ± 6.71 (10)		260.1 ± 8.40 (10)		234.9 ± 4.37 (10)		208.4 ± 5.42 (10)	+ A
WEEK 11		259.3 ± 4.02 (10)	257.2 ± 7.01 (10)		261.8 ± 7.60 (10)		238.4 ± 4.27 (10)		206.6 ± 6.19 (10)	+ A
WEEK 12		264.6 ± 4.06 (10)	262.6 ± 7.11 (10)		267.3 ± 7.45 (10)		241.3 ± 3.65 (10)		211.0 ± 5.42 (10)	+ A
WEEK 13		264.5 ± 4.92 (10)	261.9 ± 6.43 (10)		264.2 ± 8.13 (10)		239.8 ± 4.45 (10)		210.0 ± 5.81 (10)	+ A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 61

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
			TREATMENT GROUPS							
WEEK 1	+	47.05 ± 1.35 (20)	55.00 ± 1.20 (20)	+	42.80 ± 4.32 (20)		43.50 ± 2.18 (20)		11.70 ± 2.36 (20)	+ D
WEEK 2	*	53.75 ± 1.77 (20)	49.15 ± 1.42 (20)	*	50.60 ± 3.14 (20)		48.90 ± 1.85 (20)		35.30 ± 1.79 (20)	+ B
WEEK 3		37.10 ± 1.57 (20)	38.20 ± 1.73 (20)		39.25 ± 1.53 (20)		32.20 ± 1.80 (20)		35.95 ± 1.32 (20)	
WEEK 4		36.00 ± 2.19 (20)	37.85 ± 1.67 (20)		37.35 ± 1.52 (20)		37.05 ± 1.74 (20)		27.05 ± 1.67 (20)	* A
WEEK 5	+	21.93 ± 4.07 (15)	20.10 ± 1.36 (10)		21.40 ± 2.40 (10)		22.30 ± 1.97 (10)		23.90 ± 1.80 (10)	
WEEK 6	+	18.67 ± 4.97 (15)	20.40 ± 1.47 (10)		23.00 ± 1.84 (10)		21.70 ± 1.16 (10)		7.80 ± 2.72 (10)	A
WEEK 7		22.20 ± 1.55 (15)	15.50 ± 1.10 (10)	* A	15.70 ± 1.23 (10)	* A	19.10 ± 1.63 (10)		16.10 ± 1.27 (10)	A
WEEK 8		20.93 ± 1.64 (15)	20.30 ± 2.04 (10)		20.50 ± 2.07 (10)		19.40 ± 2.02 (10)		15.20 ± 2.15 (10)	
WEEK 9		11.20 ± 2.64 (10)	-4.30 ± 2.13 (10)	+ D	-4.30 ± 3.95 (10)	+ D	4.70 ± 2.63 (10)		9.10 ± 2.06 (10)	
WEEK 10	*	16.70 ± 1.49 (10)	25.40 ± 1.31 (10)	+ A	22.80 ± 4.05 (10)	* B	23.70 ± 1.82 (10)	*	11.00 ± 2.30 (10)	
WEEK 11		9.50 ± 1.23 (10)	8.00 ± 1.00 (10)		10.80 ± 1.13 (10)		8.30 ± 1.91 (10)		9.50 ± 2.15 (10)	
WEEK 12		15.00 ± 1.85 (10)	8.00 ± 1.72 (10)	A	8.90 ± 2.00 (10)	A	8.60 ± 1.42 (10)	A	7.80 ± 2.20 (10)	A
WEEK 13		6.60 ± 4.08 (10)	7.50 ± 3.66 (10)	•	5.60 ± 4.55 (10)	•	5.30 ± 3.56 (10)	•	-2.00 ± 2.80 (10)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 62

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T P	.05 % IN DIET	T R	.25 % IN DIET	T R
WEEK 1		17.10 ± 1.33 (20)	20.80 ± 1.48 (20)		22.05 ± 1.16 (20)		20.50 ± 1.07 (20)		-.10 ± 1.11 (20)	+ D
WEEK 2		21.15 ± .782 (20)	15.60 ± 1.19 (20)	+ A	17.60 ± .916 (20)		13.80 ± .848 (20)	+ B	14.20 ± .972 (20)	+ B
WEEK 3		11.25 ± .962 (20)	9.70 ± 1.19 (20)		13.00 ± .754 (20)		10.40 ± .966 (20)		12.05 ± 1.12 (20)	
WEEK 4	*	11.00 ± 1.01 (20)	17.00 ± 1.24 (20)	+ A	11.65 ± 1.33 (20)		11.40 ± 1.02 (20)		8.35 ± .595 (20)	*
WEEK 5	+	6.60 ± 1.54 (15)	9.20 ± 1.07 (10)		8.10 ± 1.49 (10)		11.80 ± 1.05 (10)	*	10.90 ± 3.89 (10)	
WEEK 6	+	13.20 ± 3.85 (15)	7.50 ± 1.18 (10)		16.10 ± 5.80 (10)		3.20 ± .680 (10)	* D	2.00 ± 4.06 (10)	A
WEEK 7	+	1.67 ± 4.32 (15)	8.20 ± 1.42 (10)	•	3.30 ± 6.41 (10)	•	6.50 ± 1.08 (10)	•	5.20 ± .867 (10)	•
WEEK 8		7.93 ± 1.28 (15)	8.50 ± 1.61 (10)		4.70 ± 1.13 (10)		9.70 ± 1.29 (10)		4.30 ± 1.31 (10)	
WEEK 9		.40 ± 1.65 (10)	-6.20 ± 2.48 (10)	•	-3.50 ± 1.44 (10)	•	-1.40 ± 1.60 (10)	•	2.80 ± .879 (10)	•
WEEK 10		5.90 ± 2.02 (10)	15.20 ± 2.25 (10)	*	11.50 ± 1.71 (10)		5.60 ± 2.27 (10)		3.90 ± 1.64 (10)	
WEEK 11		4.70 ± 1.42 (10)	1.60 ± 1.68 (10)		1.70 ± 1.03 (10)		3.50 ± .833 (10)		-1.80 ± 1.74 (10)	* D
WEEK 12		5.30 ± 1.45 (10)	5.40 ± 2.13 (10)		5.50 ± 1.41 (10)		2.90 ± 1.28 (10)		4.40 ± 1.12 (10)	
WEEK 13		-.10 ± 3.46 (10)	-.70 ± 2.98 (10)	•	-3.10 ± 3.11 (10)	•	-1.50 ± 2.61 (10)	•	-1.00 ± 2.02 (10)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST [illegible] - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 63

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF MALE RATS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
INITIAL		168.2 ± 1.67 (20)	166.6 ± 4.11 (5)		170.6 ± 4.38 (5)		156.4 ± 2.87 (5)		173.8 ± 2.25 (5)	
WEEK 1		215.3 ± 2.32 (20)	224.0 ± 6.04 (5)		218.4 ± 4.41 (5)		198.0 ± 5.12 (5)		187.6 ± 6.95 (5)	+
WEEK 2		269.0 ± 3.10 (20)	279.4 ± 8.05 (5)		267.0 ± 4.38 (5)		247.6 ± 4.83 (5)		227.6 ± 9.01 (5)	+ A
WEEK 3		306.1 ± 3.58 (20)	317.4 ± 11.0 (5)		305.8 ± 5.88 (5)		279.4 ± 6.07 (5)		261.4 ± 7.46 (5)	+
WEEK 4		342.1 ± 5.22 (20)	353.8 ± 10.4 (5)		341.6 ± 7.43 (5)		313.4 ± 3.54 (5)		288.0 ± 7.23 (5)	+
WEEK 5		371.1 ± 6.24 (15)	374.2 ± 11.2 (5)		365.2 ± 10.6 (5)		343.4 ± 2.73 (5)		333.4 ± 6.79 (5)	*
WEEK 6		389.7 ± 7.49 (15)	392.6 ± 13.0 (5)		389.6 ± 11.6 (5)		364.6 ± 4.07 (5)		360.0 ± 6.98 (5)	
WEEK 7		411.9 ± 8.52 (15)	416.8 ± 13.4 (5)		404.8 ± 12.3 (5)		387.2 ± 4.93 (5)		380.2 ± 6.26 (5)	
WEEK 8		432.9 ± 9.66 (15)	443.8 ± 15.3 (5)		428.4 ± 11.6 (5)		414.2 ± 4.31 (5)		403.8 ± 8.06 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF FEMALE RATS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
INITIAL		158.1 ± 1.49 (20)	149.8 ± 2.44 (5)		155.0 ± 2.76 (5)		151.4 ± 3.27 (5)		148.4 ± 3.30 (5)	
WEEK 1		175.1 ± 1.69 (20)	170.6 ± 5.41 (5)		179.8 ± 3.57 (5)		173.0 ± 2.88 (5)		148.8 ± 3.01 (5)	+ A
WEEK 2		196.3 ± 1.80 (20)	187.6 ± 8.77 (5)		198.2 ± 2.44 (5)		186.8 ± 4.59 (5)		164.8 ± 4.37 (5)	+ A
WEEK 3		207.6 ± 1.81 (20)	195.4 ± 9.04 (5)		209.6 ± 3.14 (5)		199.8 ± 5.24 (5)		176.6 ± 3.87 (5)	+
WEEK 4		218.6 ± 1.85 (20)	213.4 ± 9.72 (5)		220.4 ± 4.50 (5)		210.0 ± 6.21 (5)		185.0 ± 3.36 (5)	+ A
WEEK 5		223.5 ± 2.61 (15)	217.2 ± 11.5 (5)		231.6 ± 5.46 (5)		221.4 ± 6.45 (5)		206.8 ± 5.00 (5)	
WEEK 6		236.7 ± 4.28 (15)	232.4 ± 8.13 (5)		242.6 ± 6.62 (5)		231.8 ± 6.72 (5)		213.2 ± 4.50 (5)	
WEEK 7		238.3 ± 2.77 (15)	239.4 ± 7.64 (5)		249.0 ± 6.91 (5)		234.6 ± 7.05 (5)		222.0 ± 4.94 (5)	
WEEK 8		246.3 ± 3.09 (15)	246.0 ± 7.69 (5)		258.0 ± 8.12 (5)		249.6 ± 7.21 (5)		233.2 ± 4.87 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 65

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF MALE RATS DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
INITIAL		168.2 ± 1.67 (20)	169.0 ± 3.00 (5)		166.0 ± 3.21 (5)		174.2 ± 3.47 (5)		167.2 ± 3.17 (5)	
WEEK 1	*	215.3 ± 2.32 (20)	225.8 ± 2.08 (5)	*	211.8 ± 3.38 (5)		216.6 ± 9.36 (5)		177.0 ± 2.93 (5)	+ A
WEEK 2	*	269.0 ± [illegible].10 (20)	273.2 ± 2.65 (5)		268.4 ± 3.66 (5)		271.0 ± 12.0 (5)		212.8 ± 6.00 (5)	+ A
WEEK 3		306.1 ± 3.58 (20)	306.0 ± 6.20 (5)		304.6 ± 3.66 (5)		301.2 ± 10.2 (5)		250.8 ± 4.48 (5)	+ A
WEEK 4		342.1 ± 5.22 (20)	337.2 ± 9.24 (5)		347.2 ± 6.13 (5)		343.4 ± 10.6 (5)		275.4 ± 3.68 (5)	+ A
WEEK 5		371.1 ± 6.24 (15)	355.2 ± 10.8 (5)		371.6 ± 7.42 (5)		367.0 ± 11.7 (5)		297.2 ± 4.69 (5)	+ A
WEEK 6		389.7 ± 7.49 (15)	374.8 ± 12.3 (5)		394.0 ± 9.45 (5)		390.0 ± 12.2 (5)		302.2 ± 6.67 (5)	+ A
WEEK 7		411.9 ± 8.52 (15)	389.0 ± 12.0 (5)		408.6 ± 10.6 (5)		408.6 ± 14.2 (5)		318.2 ± 8.43 (5)	+ A
WEEK 8		432.9 ± 9.66 (15)	411.4 ± 13.6 (5)		428.0 ± 13.1 (5)		428.2 ± 14.3 (5)		335.8 ± 7.25 (5)	+ A
WEEK 9		451.7 ± 13.0 (10)	405.2 ± 14.4 (5)		432.2 ± 9.90 (5)		428.6 ± 13.2 (5)		344.6 ± 7.90 (5)	+ A
WEEK 10		468.4 ± 13.0 (10)	430.2 ± 15.5 (5)		456.0 ± 10.6 (5)		453.4 ± 14.7 (5)		353.6 ± 7.76 (5)	+ A
WEEK 11		477.9 ± 13.0 (10)	440.2 ± 16.6 (5)		465.8 ± 11.9 (5)		464.2 ± 16.6 (5)		366.2 ± 10.9 (5)	+ A
WEEK 12		492.9 ± 13.3 (10)	449.8 ± 18.7 (5)		473.0 ± 12.3 (5)		471.2 ± 18.0 (5)		371.2 ± 11.1 (5)	+ A
WEEK 13		499.5 ± 14.7 (10)	457.8 ± 18.7 (5)		489.6 ± 12.1 (5)		485.6 ± 20.0 (5)		377.2 ± 10.7 (5)	+ A
WEEK 14		521.4 ± 14.9 (5)	475.2 ± 18.3 (5)		494.0 ± 13.1 (5)		506.6 ± 20.4 (5)		411.4 ± 12.6 (5)	+ A
WEEK 15		537.4 ± 16.8 (5)	490.6 ± 21.2 (5)		509.6 ± 13.2 (5)		516.6 ± 20.7 (5)		437.6 ± 14.1 (5)	*
WEEK 16		538.8 ± 15.7 (5)	493.8 ± 22.9 (5)		510.8 ± 12.9 (5)		530.2 ± 21.3 (5)		451.0 ± 13.8 (5)	*
WEEK 17		520.2 ± 15.0 (5)	482.6 ± 23.1 (5)		504.0 ± 13.3 (5)		[illegible] (5)		435.2 ± 15.4 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 66

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
INITIAL		158.1 ± 1.49 (20)	146.0 ± 2.95 (5)	*	153.0 ± 2.43 (5)		142.6 ± 2.82 (5)	+	149.0 ± 2.65 (5)	
WEEK 1		175.1 ± 1.69 (20)	167.8 ± 3.53 (5)		173.6 ± 4.97 (5)		161.8 ± 4.09 (5)		147.8 ± 3.72 (5)	+ A
WEEK 2		196.3 ± 1.80 (20)	181.0 ± 4.64 (5)	*	193.0 ± 5.42 (5)		173.4 ± 4.48 (5)	+	160.6 ± 4.09 (5)	+ A
WEEK 3		207.6 ± 1.81 (20)	193.8 ± 6.08 (5)		206.8 ± 6.96 (5)		186.0 ± 4.04 (5)	+	172.0 ± 5.99 (5)	+ A
WEEK 4		216.6 ± 1.85 (20)	206.2 ± 7.36 (5)		216.2 ± 7.11 (5)		195.4 ± 5.42 (5)	*	180.4 ± 6.39 (5)	+ A
WEEK 5		223.5 ± 2.61 (15)	215.6 ± 7.88 (5)		224.6 ± 8.82 (5)		208.2 ± 4.89 (5)		190.0 ± 6.48 (5)	+
WEEK 6		236.7 ± 4.28 (15)	224.8 ± 7.72 (5)		233.4 ± 9.66 (5)		211.6 ± 5.58 (5)		194.2 ± 6.25 (5)	+ A
WEEK 7		238.3 ± 2.77 (15)	232.6 ± 8.68 (5)		241.8 ± 9.85 (5)		219.8 ± 5.22 (5)		198.8 ± 7.11 (5)	+ A
WEEK 8		246.3 ± 3.09 (15)	238.2 ± 8.55 (5)		249.2 ± 9.95 (5)		228.2 ± 6.95 (5)		204.8 ± 8.13 (5)	+ A
WEEK 9		248.7 ± 4.74 (10)	233.6 ± 9.82 (5)		245.2 ± 8.31 (5)		228.4 ± 5.20 (5)		207.8 ± 6.81 (5)	+
WEEK 10		254.6 ± 3.85 (10)	247.2 ± 9.22 (5)		258.0 ± 11.1 (5)		233.2 ± 6.51 (5)		208.8 ± 6.55 (5)	+ A
WEEK 11		259.3 ± 4.0[illegible] (10)	247.6 ± 10.2 (5)		259.4 ± 10.5 (5)		236.4 ± 6.09 (5)		210.2 ± 8.25 (5)	+ A
WEEK 12		264.6 ± 4.06 (10)	253.0 ± 10.4 (5)		265.6 ± 9.93 (5)		240.4 ± 5.64 (5)		213.0 ± 7.05 (5)	+ A
WEEK 13		264.5 ± 4.92 (10)	260.6 ± 10.3 (5)		270.8 ± 11.6 (5)		246.0 ± 6.42 (5)		217.6 ± 6.91 (5)	+ A
WEEK 14		274.0 ± 4.69 (5)	260.4 ± 10.2 (5)		277.6 ± 11.8 (5)		251.0 ± 6.72 (5)		230.4 ± 7.62 (5)	*
WEEK 15		278.8 ± 4.22 (5)	268.2 ± 10.2 (5)		280.2 ± 11.3 (5)		262.6 ± 7.37 (5)		243.4 ± 8.58 (5)	
WEEK 16		277.2 ± 4.93 (5)	268.6 ± 12.0 (5)		280.4 ± 10.8 (5)		265.8 ± 8.24 (5)		247.6 ± 8.90 (5)	
WEEK 17		271.6 ± 4.11 (5)	259.0 ± 10.7 (5)		268.8 ± 11.4 (5)		254.6 ± 7.59 (5)		238.0 ± 10.5 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE : T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 67

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF MALE RATS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
WEEK 1		47.05 ± 1.35 (20)	57.40 ± 2.25 (5)		47.80 ± 2.60 (5)		41.60 ± 2.48 (5)		13.80 ± 5.02 (5)	+ D
WEEK 2		53.75 ± 1.77 (20)	55.40 ± 2.36 (5)		48.60 ± 2.56 (5)		49.60 ± 2.79 (5)		40.00 ± 2.83 (5)	* A
WEEK 3		37.10 ± 1.57 (20)	38.00 ± 3.94 (5)		38.80 ± 2.56 (5)		31.80 ± 3.02 (5)		33.80 ± 2.27 (5)	
WEEK 4		36.00 ± 2.19 (20)	35.40 ± 2.09 (5)		35.80 ± 2.78 (5)		34.00 ± 2.70 (5)		26.60 ± 5.05 (5)	
WEEK 5	+	21.93 ± 4.07 (15)	20.40 ± 1.08 (5)		23.60 ± 3.70 (5)		30.00 ± 1.45 (5)		45.40 ± 2.32 (5)	+ A
WEEK 6	+	18.67 ± 4.97 (15)	18.40 ± 2.20 (5)		24.40 ± 1.40 (5)		21.20 ± 2.08 (5)		26.60 ± 2.04 (5)	
WEEK 7		22.20 ± 1.55 (15)	24.20 ± 2.42 (5)		15.20 ± 1.88 (5)		22.60 ± 2.11 (5)		20.20 ± 1.28 (5)	
WEEK 8		20.93 ± 1.64 (15)	27.00 ± 2.21 (5)		23.60 ± .678 (5)		27.00 ± 2.76 (5)		23.60 ± 4.01 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 68

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF FEMALE RATS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
WEEK 1		17.10 ± 1.33 (20)	20.80 ± 4.32 (5)		24.80 ± 2.46 (5)		21.60 ± 1.03 (5)		.40 ± 2.54 (5)	+ D
WEEK 2		21.15 ± .782 (20)	17.00 ± 3.59 (5)		18.40 ± 1.33 (5)		13.80 ± 1.77 (5)	* A	16.00 ± 2.32 (5)	
WEEK 3		11.25 ± .962 (20)	7.80 ± 1.28 (5)		11.40 ± 1.69 (5)		13.00 ± .775 (5)		11.80 ± 2.37 (5)	
WEEK 4		11.00 ± 1.01 (20)	18.00 ± .775 (5)	A	10.80 ± 2.85 (5)		10.20 ± 1.66 (5)		8.40 ± 1.44 (5)	
WEEK 5		6.60 ± 1.54 (15)	3.80 ± 1.96 (5)		11.20 ± 1.32 (5)		11.40 ± 1.60 (5)		21.80 ± 2.20 (5)	+ D
WEEK 6	+	13.20 ± 3.85 (15)	15.20 ± 3.87 (5)		11.00 ± 1.76 (5)		10.40 ± 1.17 (5)		6.40 ± .927 (5)	A
WEEK 7	+	1.67 ± 4.32 (15)	7.00 ± 2.21 (5)	•	6.40 ± 1.08 (5)	•	2.80 ± 2.03 (5)	•	8.80 ± .860 (5)	•
WEEK 8		7.93 ± 1.28 (15)	6.60 ± 2.06 (5)		9.00 ± 2.74 (5)		15.00 ± 1.52 (5)		11.20 ± 1.11 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 69

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF MALE RATS DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
WEEK 1	*	47.05 ± 1.35 (20)	56.80 ± 1.39 (5)	+ A	45.80 ± 3.60 (5)		42.40 ± 7.33 (5)		9.80 ± 3.12 (5)	+ D
WEEK 2		53.75 ± 1.77 (20)	47.40 ± 2.60 (5)		56.60 ± 2.66 (5)		54.40 ± 3.82 (5)		35.80 ± 3.35 (5)	+ A
WEEK 3		37.10 ± 1.57 (20)	32.80 ± 3.85 (5)		36.20 ± 2.08 (5)		30.20 ± 4.73 (5)		38.00 ± 2.47 (5)	
WEEK 4		36.00 ± 2.19 (20)	31.20 ± 3.64 (5)		4[illegible].60 ± 2.84 (5)		42.2[illegible] ± 4.87 (5)		24.60 ± 1.94 (5)	
WEEK 5	*	21.93 ± 4.07 (15)	18.00 ± 1.73 (5)		24.40 ± 2.04 (5)		23.60 ± 2.66 (5)		21.80 ± 2.96 (5)	
WEEK 6	+	18.67 ± 4.97 (15)	19.60 ± 2.38 (5)		22.40 ± 2.54 (5)		23.00 ± 1.[illegible]5 (5)		5.00 ± 4.46 (5)	A
WEEK 7		22.20 ± 1.55 (15)	14.20 ± [illegible].66 (5)	A	14.60 ± 2.25 (5)	A	18.60 ± 2.3[illegible] (5)		16.00 ± 2.05 (5)	
WEEK 8		20.93 ± 1.64 (15)	22.40 ± 3.36 (5)		19.40 ± 3.79 (5)		19.60 ± 2.19 (5)		17.60 ± 2.42 (5)	
WEEK 9		11.20 ± 2.64 (10)	-6.20 ± 3.56 (5)	* D	4.20 ± 4.53 (5)		.40 ± 3.49 (5)	B	8.80 ± 2.27 (5)	
WEEK 10		16.70 ± 1.49 (10)	25.00 ± [illegible].64 (5)		23.80 ± 2.58 (5)		24.80 ± 2.31 (5)		9.00 ± 2.57 (5)	A
WEEK 11		9.55 ± 1.23 (10)	10.00 ± 1.30 (5)		9.80 ± 1.59 (5)		10.80 ± 3.06 (5)		12.60 ± 3.19 (5)	
WEEK 12		15.00 ± 1.85 (10)	9.60 ± 2.60 (5)		7.20 ± 2.08 (5)	A	7.00 ± 2.17 (5)	A	5.00 ± 1.67 (5)	* B
WEEK 13	*	6.60 ± 4.08 (10)	18.00 ± 1.45 (5)	* [illegible]	16.60 ± 2.84 (5)	•	14.40 ± 3.17 (5)	•	6.00 ± 1.52 (5)	•
WEEK 14		.60 ± 2.50 (5)	7.40 ± 1.91 (5)	•	4.40 ± 2.32 (5)	•	21.00 ± 2.59 (5)	•	34.20 ± 3.51 (5)	+ •
WEEK 15		16.00 ± 2.88 (5)	15.40 ± 3.96 (5)		15.60 ± 1.75 (5)		10.00 ± 2.85 (5)		26.20 ± 1.77 (5)	
WEEK 16		1.40 ± 1.40 (5)	3.20 ± 1.93 (5)	•	1.20 ± 2.08 (5)	•	13.60 ± 2.[illegible]0 (5)	+ •	13.40 ± 2.29 (5)	+ •
WEEK 17	*	-18.60 ± 6.00 (5)	-11.20 ± 3.31 (5)	•	-[illegible].80 ± .583 (5)	•	-16.60 ± 3.56 (5)	•	-15.80 ± 2.33 (5)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - •

TABLE 70

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	.062 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
			TREATMENT GROUPS							
WEEK 1		17.10 ± 1.33 (20)	21.80 ± 1.62 (5)		20.60 ± 3.22 (5)		19.20 ± 1.59 (5)		-1.20 ± 1.77 (5)	+ D
WEEK 2		21.15 ± .782 (20)	13.20 ± 1.56 (5)	+ B	19.40 ± 2.01 (5)		11.60 ± .812 (5)	+ B	12.80 ± 1.39 (5)	+ B
WEEK 3		11.25 ± .962 (20)	12.80 ± 2.42 (5)		13.80 ± 1.77 (5)		12.60 ± 1.03 (5)		11.40 ± 2.01 (5)	
WEEK 4		11.00 ± 1.01 (20)	12.40 ± 1.44 (5)		9.40 ± 1.29 (5)		9.40 ± 1.40 (5)		8.40 ± .872 (5)	
WEEK 5	+	6.50 ± 1.54 (15)	9.40 ± .980 (5)		8.40 ± 2.01 (5)		12.80 ± 1.74 (5)	*	9.60 ± 7.93 (5)	
WEEK 6	*	13.20 ± 3.85 (15)	9.20 ± 2.06 (5)		8.80 ± 1.83 (5)		3.40 ± 1.08 (5)	* D	4.20 ± 8.15 (5)	
WEEK 7	+	1.67 ± 4.32 (15)	7.80 ± 2.18 (5)	•	9.40 ± .678 (5)	•	8.20 ± 1.71 (5)	•	4.60 ± 1.03 (5)	•
WEEK 8		7.93 ± 1.28 (15)	5.60 ± 1.50 (5)		7.40 ± 1.44 (5)		8.40 ± 2.44 (5)		6.00 ± 2.10 (5)	
WEEK 9		.40 ± 1.65 (10)	-4.60 ± 1.83 (5)	•	-4.00 ± 2.28 (5)	•	.20 ± 2.82 (5)	•	3.00 ± 1.64 (5)	•
WEEK 10		5.90 ± 2.02 (10)	13.60 ± 2.20 (5)		12.80 ± 3.12 (5)		4.80 ± 2.22 (5)		1.00 ± 2.21 (5)	
WEEK 11		4.70 ± 1.42 (10)	.40 ± 2.82 (5)		1.40 ± .678 (5)		3.20 ± 1.46 (5)		1.40 ± 2.32 (5)	
WEEK 12		5.30 ± 1.45 (10)	5.40 ± 1.63 (5)		6.20 ± .860 (5)		4.00 ± .707 (5)		2.80 ± 1.39 (5)	
WEEK 13	+	-.10 ± 3.46 (10)	7.60 ± .812 (5)		5.20 ± 2.03 (5)	D	5.60 ± 1.33 (5)	C	4.60 ± .927 (5)	C
WEEK 14		-2.60 ± 1.03 (5)	-.20 ± 1.32 (5)	•	6.80 ± 2.03 (5)	+ •	5.00 ± 1.95 (5)	* •	12.80 ± 1.16 (5)	+ •
WEEK 15		4.80 ± 1.36 (5)	7.80 ± 1.28 (5)		2.60 ± .678 (5)		11.60 ± 2.84 (5)		13.00 ± 2.02 (5)	
WEEK 16		-1.60 ± 1.63 (5)	.40 ± 1.94 (5)	•	.20 ± 1.50 (5)	•	3.20 ± 2.27 (5)	D	4.20 ± 1.83 (5)	
WEEK 17	*	-5.60 ± 3.20 (5)	-9.60 ± 9.39 (5)	•	-11.60 ± 1.69 (5)		-11.20 ± 2.11 (5)		-9.60 ± 2.20 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 71

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .002 % IN DIET		W	.01 % IN DIET		W	.05 % IN DIET		W	.25 % IN DIET		W
WEEK 1	20.7 ± .502	(8)	20.4 ± .308	(8)		19.1 ± .776	(8)		18.5 ± .347	(8)	*	11.6 ± .715	(8)	*
WEEK 2	24.3 ± .433	(8)	25.5 ± .419	(8)		25.1 ± .661	(8)		24.4 ± .650	(8)		18.3 ± .858	(8)	*
WEEK 3	27.1 ± .724	(8)	26.9 ± .360	(8)		26.6 ± .580	(8)		25.1 ± .489	(8)		20.8 ± .656	(8)	*
WEEK 4	27.7 ± .922	(8)	27.1 ± .395	(8)		26.2 ± .585	(8)		24.9 ± .615	(8)	*	20.9 ± .505	(8)	*
WEEK 5	29.0 ± .844	(6)	26.2 ± .055	(4)		25.8 ± 1.29	(4)		25.5 ± .429	(4)	*	20.2 ± .790	(4)	*
WEEK 6	26.8 ± .835	(6)	26.8 ± .255	(4)		25.3 ± 1.06	(4)		26.3 ± .901	(4)		19.5 ± .975	(4)	*
WEEK 7	28.6 ± 1.13	(6)	26.7 ± .365	(4)		26.2 ± .759	(4)		26.2 ± 1.05	(4)		19.4 ± .447	(4)	*
WEEK 8	28.7 ± 1.13	(6)	24.7 ± .499	(4)	*	26.3 ± .544	(4)		25.6 ± .670	(4)		19.3 ± .703	(4)	*
WEEK 9	25.3 ± .561	(4)	23.0 ± .150	(3)		24.0 ± 1.06	(4)		24.6 ± .842	(4)		19.4 ± .796	(4)	*
WEEK 10	27.3 ± .777	(4)	25.3 ± .201	(4)		27.0 ± .431	(4)		26.4 ± .898	(4)		19.9 ± .709	(4)	*
WEEK 11	26.6 ± .809	(4)	25.2 ± .204	(4)		25.6 ± .826	(4)		25.3 ± .556	(4)		19.2 ± .764	(4)	*
WEEK 12	29.4 ± .805	(4)	26.0 ± .482	(4)		26.3 ± 1.17	(4)		27.4 ± 1.64	(4)		20.7 ± .870	(4)	*
WEEK 13	31.5 ± .508	(4)	27.3 ± .712	(4)	*	27.5 ± 1.11	(4)	*	26.9 ± .762	(4)	*	19.7 ± .703	(4)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 72

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	15.9 ± .288 (8)	14.5 ± .586 (8)		15.2 ± .323 (8)		13.1 ± .450 (8)	*	8.1 ± .338 (8)	*
WEEK 2	17.0 ± .373 (8)	16.8 ± .480 (8)		17.6 ± .253 (8)		16.4 ± .411 (8)		13.4 ± .299 (8)	*
WEEK 3	16.7 ± .228 (8)	17.5 ± .235 (8)		17.7 ± .419 (8)		16.4 ± .418 (8)		13.5 ± .196 (8)	*
WEEK 4	16.0 ± .688 (8)	16.9 ± .237 (8)		16.6 ± .510 (8)		15.9 ± .481 (8)		13.1 ± .289 (8)	*
WEEK 5	18.4 ± 1.46 (6)	16.7 ± .437 (4)		17.2 ± .251 (4)		15.1 ± .470 (4)		13.3 ± .747 (4)	*
WEEK 6	16.7 ± .360 (6)	16.3 ± .305 (4)		18.1 ± .570 (4)		15.9 ± .434 (4)		13.0 ± .394 (4)	*
WEEK 7	15.5 ± .363 (6)	16.4 ± .555 (4)		17.9 ± .601 (4)		15.7 ± .423 (4)		12.3 ± .452 (4)	*
WEEK 8	16.6 ± .371 (6)	16.4 ± .486 (4)		16.9 ± .528 (4)		15.6 ± .408 (4)		12.2 ± .437 (4)	*
WEEK 9	14.8 ± .233 (4)	14.5 ± .329 (4)		16.6 ± .654 (4)		15.1 ± .338 (4)		12.5 ± .639 (4)	*
WEEK 10	16.5 ± .215 (4)	16.9 ± .807 (4)		17.1 ± .584 (4)		16.4 ± .792 (4)		12.6 ± .822 (4)	*
WEEK 11	16.5 ± .355 (4)	15.8 ± .583 (4)		16.0 ± .454 (4)		15.3 ± .551 (4)		11.9 ± .741 (4)	*
WEEK 12	17.6 ± 1.09 (4)	16.9 ± .768 (4)		17.9 ± .765 (4)		15.4 ± .595 (4)		13.7 ± 1.31 (4)	
WEEK 13	18.3 ± .454 (4)	17.7 ± .512 (4)		18.8 ± .684 (4)		16.7 ± .696 (4)		13.1 ± .310 (4)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 73

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	96.2 ± 1.13 (8)	92.6 ± 1.40 (8)		90.6 ± 2.18 (8)		87.0 ± .899 (8)	*	63.6 ± 2.19 (8)	*
WEEK 2	90.2 ± .365 (8)	94.4 ± .895 (8)		95.9 ± 1.51 (8)		93.3 ± 1.12 (8)		84.1 ± 1.72 (8)	*
WEEK 3	88.4 ± 1.17 (8)	87.5 ± .790 (8)		88.7 ± 1.39 (8)		85.7 ± .996 (8)		82.2 ± 1.03 (8)	*
WEEK 4	81.0 ± 1.36 (8)	78.3 ± .576 (8)		77.5 ± 1.19 (8)		75.4 ± .840 (8)	*	74.7 ± .569 (8)	*
WEEK 5	78.3 ± 2.29 (6)	73.2 ± .525 (4)		71.5 ± 2.53 (4)		71.9 ± .918 (4)		68.7 ± .444 (4)	*
WEEK 6	68.8 ± 1.02 (6)	70.7 ± .631 (4)		65.8 ± 1.89 (4)		69.8 ± 1.28 (4)		64.4 ± .762 (4)	
WEEK 7	69.4 ± 1.51 (6)	67.7 ± 1.20 (4)		65.5 ± 1.11 (4)		66.0 ± 1.41 (4)		61.1 ± .903 (4)	*
WEEK 8	66.2 ± 2.85 (6)	59.7 ± .714 (4)		62.6 ± .653 (4)		61.7 ± 1.11 (4)		57.8 ± .272 (4)	*
WEEK 9	56.1 ± .760 (4)	56.1 ± .260 (3)		57.7 ± 1.68 (4)		58.5 ± 1.37 (4)		56.7 ± .542 (4)	
WEEK 10	58.3 ± .648 (4)	58.0 ± .287 (4)		60.2 ± 1.14 (4)		59.4 ± 1.24 (4)		56.2 ± .493 (4)	
WEEK 11	55.7 ± .287 (4)	56.8 ± .685 (4)		55.6 ± .991 (4)		56.1 ± 1.90 (4)		52.9 ± .476 (4)	
WEEK 12	59.8 ± 2.61 (4)	57.6 ± 1.03 (4)		56.1 ± 1.82 (4)		59.5 ± 3.01 (4)		55.6 ± 1.16 (4)	
WEEK 13	62.8 ± 1.51 (4)	59.4 ± 1.92 (4)		58.0 ± 2.61 (4)		57.9 ± 2.07 (4)		53.5 ± 1.05 (4)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 74

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	90.8 ± .976 (8)	84.0 ± 2.97 (8)		86.8 ± 1.33 (8)		77.4 ± 2.29 (8)	*	54.8 ± 1.93 (8)	*
WEEK 2	86.4 ± 1.84 (8)	89.4 ± 2.16 (8)		91.4 ± 1.57 (8)		89.9 ± 1.17 (8)		83.4 ± 1.06 (8)	
WEEK 3	80.4 ± .713 (8)	88.2 ± .789 (8)		86.1 ± 1.73 (8)		85.2 ± 1.77 (8)		78.3 ± 1.05 (8)	
WEEK 4	73.0 ± 2.85 (8)	78.7 ± .713 (8)		76.4 ± 2.11 (8)		77.7 ± 1.46 (8)		72.1 ± .965 (8)	
WEEK 5	82.6 ± 7.46 (6)	75.1 ± 1.04 (4)		75.7 ± 1.93 (4)		71.6 ± 1.81 (4)		69.6 ± 2.94 (4)	
WEEK 6	70.7 ± 1.75 (6)	71.0 ± .930 (4)		74.4 ± 3.53 (4)		74.2 ± 1.39 (4)		67.7 ± .826 (4)	
WEEK 7	65.1 ± 1.20 (6)	68.8 ± 1.43 (4)		72.7 ± 3.87 (4)		71.0 ± 1.40 (4)		62.4 ± .646 (4)	
WEEK 8	67.6 ± 1.59 (6)	66.3 ± .872 (4)		67.1 ± 2.80 (4)		67.7 ± 1.31 (4)		60.6 ± .456 (4)	*
WEEK 9	59.7 ± 1.09 (4)	60.4 ± .602 (4)		66.8 ± 3.46 (4)		65.7 ± 1.29 (4)		60.9 ± 1.57 (4)	
WEEK 10	65.1 ± 2.35 (4)	66.0 ± 2.19 (4)		65.7 ± 2.17 (4)		69.8 ± 3.05 (4)		60.4 ± 1.88 (4)	
WEEK 11	63.5 ± .881 (4)	61.5 ± .854 (4)		61.3 ± 2.41 (4)		64.0 ± 1.82 (4)		57.3 ± 2.09 (4)	
WEEK 12	66.5 ± 2.77 (4)	64.3 ± 1.55 (4)		67.0 ± 2.21 (4)		63.9 ± 1.98 (4)		65.0 ± 6.14 (4)	
WEEK 13	69.0 ± 3.53 (4)	67.7 ± 1.74 (4)		71.3 ± 3.35 (4)		69.8 ± 2.43 (4)		62.5 ± .846 (4)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 75

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE RATS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	20.7 ± .502 (8)	21.7 ± .513 (2)		20.5 ± 1.99 (2)		17.7 ± .595 (2)		12.6 ± .933 (2)	*
WEEK 2	24.3 ± .433 (8)	26.5 ± .851 (2)		27.1 ± 1.06 (2)		23.0 ± .525 (2)		18.7 ± 1.03 (2)	*
WEEK 3	27.1 ± .724 (8)	27.4 ± 1.31 (2)		27.5 ± .840 (2)		24.8 ± .560 (2)		21.5 ± .187 (2)	*
WEEK 4	27.7 ± .922 (8)	28.2 ± 1.55 (2)		27.3 ± 1.31 (2)		23.6 ± .980 (2)		21.4 ± .688 (2)	*
WEEK 5	29.0 ± .844 (6)	28.3 ± 1.29 (2)		28.7 ± 2.16 (2)		25.5 ± .723 (2)		26.7 ± .432 (2)	
WEEK 6	26.8 ± .835 (6)	27.5 ± 1.43 (2)		27.7 ± .840 (2)		25.6 ± .933 (2)		27.5 ± .478 (2)	
WEEK 7	28.6 ± 1.13 (6)	28.5 ± .062 (2)		28.8 ± .910 (2)		26.0 ± 1.25 (2)		27.0 ± 1.60 (2)	
WEEK 8	28.7 ± 1.13 (6)	29.2 ± 3.36 (2)		29.2 ± .677 (2)		26.8 ± .747 (2)		27.0 ± .898 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 76

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE RATS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	15.9 ± .288 (8)	14.0 ± .665	(2)	15.3 ± .583	(2)	14.4 ± .350	(2)	8.1 ± .653	(2) *
WEEK 2	17.0 ± .373 (8)	15.8 ± 2.05	(2)	17.7 ± .537	(2)	17.5 ± .490	(2)	13.7 ± .607	(2)
WEEK 3	16.7 ± .228 (8)	16.9 ± .408	(2)	17.3 ± .012	(2)	17.8 ± .152	(2)	13.9 ± .222	(2) *
WEEK 4	16.0 ± .688 (8)	16.4 ± .420	(2)	16.6 ± .572	(2)	16.8 ± .851	(2)	13.4 ± .070	(2)
WEEK 5	18.4 ± 1.46 (6)	16.9 ± .268	(2)	16.3 ± .090	(2)	17.7 ± .735	(2)	17.6 ± .397	(2)
WEEK 6	16.7 ± .360 (6)	16.8 ± .443	(2)	17.3 ± .420	(2)	17.5 ± .828	(2)	15.6 ± 1.74	(2)
WEEK 7	15.5 ± .353 (6)	16.5 ± .268	(2)	16.4 ± .385	(2)	15.9 ± .770	(2)	16.5 ± .630	(2)
WEEK 8	16.6 ± .371 (6)	16.7 ± .222	(2)	18.2 ± .898	(2)	17.4 ± .583	(2)	18.8 ± 1.60	(2)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 77

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE RATS DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	20.7 ± .502	(8)	20.0 ± .198	(2)	19.1 ± .420	(2)	18.3 ± 1.31	(2)	10.6 ± .642	(2) *
WEEK 2	24.3 ± .433	(8)	26.4 ± .117	(2)	25.9 ± .583	(2)	25.1 ± 2.73	(2)	18.1 ± 1.38	(2) *
WEEK 3	27.1 ± .724	(8)	26.8 ± 1.07	(2)	27.1 ± 2.18	(2)	25.5 ± 1.27	(2)	20.9 ± .420	(2) *
WEEK 4	27.7 ± .922	(8)	26.4 ± .058	(2)	27.0 ± 1.81	(2)	26.3 ± 1.01	(2)	20.8 ± .070	(2) *
WEEK 5	29.0 ± .844	(6)	26.2 ± .035	(2)	27.9 ± .933	(2)	25.9 ± .163	(2)	20.3 ± .152	(2) *
WEEK 6	26.8 ± .835	(6)	26.3 ± .105	(2)	26.5 ± 1.74	(2)	26.9 ± 1.64	(2)	19.2 ± .572	(2) *
WEEK 7	28.6 ± 1.13	(6)	26.7 ± .607	(2)	27.1 ± 1.17	(2)	27.2 ± 1.85	(2)	19.4 ± .408	(2) *
WEEK 8	28.7 ± 1.13	(6)	24.6 ± 1.06	(2)	26.4 ± 1.13	(2)	26.2 ± 1.38	(2)	19.5 ± .268	(2) *
WEEK 9	25.3 ± .561	(4)	22.9 ± .175	(2)	25.4 ± .840	(2)	24.9 ± 1.97	(2)	19.2 ± .222	(2) *
WEEK 10	27.3 ± .777	(4)	25.1 ± .373	(2)	26.6 ± .910	(2)	26.9 ± 1.69	(2)	20.2 ± .268	(2) *
WEEK 11	26.6 ± .809	(4)	25.4 ± .093	(2)	26.2 ± 1.80	(2)	24.8 ± 1.13	(2)	19.1 ± .023	(2) *
WEEK 12	29.4 ± .805	(4)	26.1 ± .222	(2)	26.4 ± 2.80	(2)	27.3 ± 3.36	(2)	20.1 ± 1.11	(2) *
WEEK 13	31.5 ± .508	(4)	26.6 ± .991	(2) *	26.8 ± 2.20	(2)	26.8 ± 1.82	(2)	19.5 ± .338	(2) *
WEEK 14	29.8 ± 1.50	(2)	30.5 ± 2.26	(2)	28.4 ± 1.97	(2)	33.1 ± 2.44	(2)	30.5 ± 1.25	(2)
WEEK 15	30.3 ± 1.54	(2)	28.2 ± 1.55	(2)	33.7 ± 1.07	(2)	32.0 ± 3.73	(2)	26.6 ± .385	(2)
WEEK 16	31.2 ± .373	(2)	28.2 ± 1.88	(2)	32.3 ± 1.70	(2)	33.4 ± 3.09	(2)	30.6 ± 4.02	(2)
WEEK 17	29.1 ± .082	(2)	34.0 ± 2.53	(2)	30.5 ± 1.74	(2)	33.9 ± 4.20	(2)	26.8 ± 5.24	(2)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 78

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	15.9 ± .288 (8)	15.3 ± .537 (2)		15.8 ± .245 (2)		11.9 ± .933 (2)	*	8.5 ± .630 (2)	*
WEEK 2	17.0 ± .373 (8)	16.7 ± .187 (2)		18.4 ± .455 (2)		15.5 ± .315 (2)		13.2 ± .712 (2)	*
WEEK 3	16.7 ± .228 (8)	17.[illegible] ± .513 (2)		18.9 ± .128 (2)		16.2 ± 1.33 (2)		13.3 ± .537 (2)	*
WEEK 4	16.0 ± .688 (8)	16.4 ± .128 (2)		17.4 ± .700 (2)		15.2 ± .219 (2)		13.0 ± .175 (2)	
WEEK 5	18.4 ± 1.46 (6)	16.2 ± .432 (2)		17.5 ± .152 (2)		15.1 ± 1.13 (2)		14.1 ± .117 (2)	
WEEK 6	16.7 ± .360 (6)	16.1 ± .105 (2)		17.9 ± .047 (2)		15.3 ± .653 (2)		13.4 ± .163 (2)	*
WEEK 7	15.5 ± .363 (6)	15.5 ± .478 (2)		18.6 ± .875 (2)		15.5 ± .968 (2)		12.6 ± .082 (2)	*
WEEK 8	16.6 ± .371 (6)	15.6 ± .595 (2)		17.7 ± .140 (2)		15.3 ± .875 (2)		12.6 ± .292 (2)	*
WEEK 9	14.8 ± .233 (4)	14.2 ± .035 (2)		17.3 ± .886 (2)		15.3 ± .758 (2)		13.1 ± .175 (2)	
WEEK 10	16.5 ± .215 (4)	15.7 ± .956 (2)		17.8 ± .443 (2)		16.4 ± 1.71 (2)		12.7 ± .373 (2)	*
WEEK 11	16.5 ± .355 (4)	14.9 ± .443 (2)		16.7 ± .327 (2)		15.3 ± 1.12 (2)		12.8 ± .630 (2)	*
WEEK 12	17.6 ± 1.09 (4)	15.9 ± .420 (2)		17.7 ± .152 (2)		15.6 ± 1.41 (2)		15.6 ± 1.63 (2)	
WEEK 13	18.3 ± .454 (4)	16.9 ± .070 (2)		19.6 ± .968 (2)		16.8 ± 1.56 (2)		13.4 ± .245 (2)	*
WEEK 14	19.1 ± .921 (2)	17.1 ± .886 (2)		19.4 ± 1.54 (2)		19.1 ± 1.46 (2)		19.7 ± .327 (2)	
WEEK 15	18.3 ± .945 (2)	16.6 ± .443 (2)		21.0 ± 1.90 (2)		18.4 ± 1.01 (2)		18.5 ± .455 (2)	
WEEK 16	16.6 ± .117 (2)	17.7 ± .758 (2)		22.4 ± 3.97 (2)		19.7 ± 2.86 (2)		21.9 ± .910 (2)	
WEEK 17	20.9 ± 1.45 (2)	19.8 ± 1.80 (2)		20.0 ± .435 (2)		20.9 ± 2.83 (2)		19.6 ± 1.35 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 79

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF MALE RATS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	96.2 ± 1.13 (8)	96.8 ± 1.73	(2)	93.8 ± 7.13	(2)	89.2 ± .250	(2)	66.9 ± 2.05	(2) *
WEEK 2	90.2 ± .365 (8)	94.8 ± 1.52	(2)	103.4 ± 2.75	(2)	92.9 ± 2.62	(2)	82.4 ± .039	(2) *
WEEK 3	88.4 ± 1.17 (8)	86.3 ± .232	(2)	89.8 ± 1.96	(2)	88.9 ± .048	(2)	82.3 ± 1.86	(2)
WEEK 4	81.0 ± 1.36 (8)	79.6 ± 1.48	(2)	79.9 ± 2.49	(2)	75.4 ± 2.27	(2)	74.2 ± .548	(2)
WEEK 5	78.3 ± 2.29 (6)	75.7 ± .674	(2)	78.5 ± 3.55	(2)	74.1 ± 1.42	(2)	80.4 ± 4.20	(2)
WEEK 6	68.8 ± 1.02 (6)	69.9 ± .964	(2)	71.2 ± .203	(2)	70.1 ± 2.16	(2)	76.4 ± 1.34	(2) *
WEEK 7	69.4 ± 1.51 (6)	68.3 ± 2.33	(2)	71.2 ± .631	(2)	67.2 ± 3.20	(2)	70.9 ± 2.15	(2)
WEEK 8	66.2 ± 2.85 (6)	65.6 ± 5.30	(2)	68.2 ± 2.95	(2)	64.7 ± 2.47	(2)	66.8 ± .236	(2)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 8[illegible]

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF FEMALE RATS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	90.8 ± .976	(8)	82.2 ± 1.71	(2) *	85.0 ± .113	(2)	83.4 ± 1.04	(2)	54.1 ± 4.02	(2) *
WEEK 2	86.4 ± 1.94	(8)	83.9 ± 6.67	(2)	89.2 ± 4.79	(2)	93.4 ± .668	(2)	83.0 ± .912	(2)
WEEK 3	80.4 ± .713	(8)	86.4 ± 1.88	(2)	82.8 ± 1.67	(2)	89.3 ± 1.37	(2)	78.9 ± .742	(2)
WEEK 4	73.0 ± 2.85	(8)	76.8 ± 1.56	(2)	75.5 ± 4.26	(2)	80.1 ± 1.11	(2)	72.3 ± .100	(2)
WEEK 5	82.6 ± 7.46	(6)	78.1 ± 5.38	(2)	70.4 ± 2.18	(2)	79.9 ± .707	(2)	85.2 ± 1.98	(2)
WEEK 6	70.7 ± 1.75	(6)	72.4 ± .025	(2)	71.5 ± 1.23	(2)	75.5 ± .979	(2)	73.4 ± 8.63	(2)
WEEK 7	65.1 ± 1.30	(6)	68.8 ± 2.41	(2)	66.0 ± 3.97	(2)	67.9 ± 1.86	(2)	74.4 ± 2.42	(2) *
WEEK 8	67.0 ± 1.59	(6)	67.8 ± 2.85	(2)	70.6 ± 5.86	(2)	69.8 ± .251	(2)	80.7 ± 5.89	(2)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 81

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF MALE RATS DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	96.2 ± 1.13	(8)	88.5 ± .304	(2) *	90.1 ± .318	(2) *	84.2 ± 1.27	(2) *	59.7 ± 2.00	(2) *
WEEK 2	90.2 ± .365	(8)	96.8 ± 1.66	(2)	96.3 ± 1.85	(2)	92.3 ± 4.26	(2)	85.0 ± 3.00	(2)
WEEK 3	88.4 ± 1.17	(8)	87.6 ± 1.74	(2)	88.9 ± 5.84	(2)	84.7 ± .319	(2)	83.5 ± .313	(2)
WEEK 4	81.0 ± 1.36	(8)	78.4 ± 1.02	(2)	77.7 ± 3.57	(2)	76.4 ± .477	(2)	75.5 ± .397	(2)
WEEK 5	78.3 ± 2.29	(6)	73.7 ± 1.05	(2)	75.0 ± .464	(2)	70.7 ± 1.50	(2)	68.4 ± .831	(2)
WEEK 6	68.8 ± 1.02	(6)	70.3 ± 1.45	(2)	67.2 ± 2.57	(2)	69.0 ± 2.68	(2)	63.6 ± .889	(2)
WEEK 7	69.4 ± 1.51	(6)	63.8 ± 2.20	(2)	66.4 ± .999	(2)	66.5 ± 3.25	(2)	61.1 ± .250	(2)
WEEK 8	66.2 ± 2.85	(6)	59.9 ± 1.35	(2)	61.7 ± .112	(2)	61.1 ± 2.4[illegible]	(2)	58.0 ± .423	(2)
WEEK 9	56.1 ± .760	(4)	56.4 ± .057	(2)	58.8 ± .517	(2)	58.1 ± 3.31	(2)	55.8 ± .061	(2)
WEEK 10	58.3 ± .648	(4)	58.4 ± .335	(2)	56.3 ± .580	(2)	59.2 ± 2.80	(2)	57.0 ± .178	(2)
WEEK 11	55.7 ± .297	(4)	57.7 ± .670	(2)	56.2 ± 2.18	(2)	53.5 ± 1.84	(2)	52.2 ± .551	(2)
WEEK 12	59.8 ± 2.61	(4)	58.0 ± .261	(2)	55.7 ± 3.99	(2)	57.9 ± 6.16	(2)	54.2 ± 1.98	(2)
WEEK 13	62.8 ± 1.51	(4)	56.8 ± 1.55	(2)	54.3 ± 2.52	(2)	55.1 ± 3.19	(2)	51.7 ± .088	(2) *
WEEK 14	57.3 ± 4.59	(2)	64.2 ± 4.50	(2)	57.4 ± 1.73	(2)	65.3 ± 4.61	(2)	74.2 ± 1.83	(2)
WEEK 15	56.[illegible] ± 1.39	(2)	57.4 ± 2.44	(2)	66.4 ± 4.42	(2)	61.9 ± 6.88	(2)	60.8 ± .298	(2)
WEEK 16	57.9 ± .789	(2)	57.1 ± 2.92	(2)	63.3 ± 1.32	(2)	63.0 ± 5.30	(2)	67.6 ± 7.37	(2)
WEEK 17	55.9 ± .881	(2)	70.4 ± 4.28	(2)	60.5 ± 1.48	(2)	66.0 ± 7.81	(2)	61.3 ± 10.1	(2)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCE
* CONFIDENCE LEVEL = .95

TABLE 82

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	W	.01 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W
WEEK 1	90.8 ± .976 (8)	91.4 ± 1.76 (2)		91.0 ± .998 (2)		73.3 ± 6.02 (2)	*	57.3 ± 2.93 (2)	*
WEEK 2	86.4 ± 1.84 (8)	92.0 ± 1.85 (2)		95.3 ± 4.41 (2)		89.1 ± 2.07 (2)		82.2 ± 5.12 (2)	
WEEK 3	80.4 ± .713 (8)	88.0 ± 2.35 (2)		91.6 ± 1.68 (2)		87.2 ± 6.55 (2)		77.6 ± 3.68 (2)	
WEEK 4	73.0 ± 2.55 (8)	79.4 ± .716 (2)		80.8 ± 6.13 (2)		77.6 ± .556 (2)		72.1 ± 1.93 (2)	
WEEK 5	82.6 ± 7.46 (6)	75.0 ± 1.55 (2)		78.3 ± 3.11 (2)		72.5 ± 4.18 (2)		7[illegible].4 ± .509 (2)	
WEEK 6	70.7 ± 1.75 (6)	71.6 ± .363 (2)		77.0 ± 3.33 (2)		72.5 ± 2.12 (2)		68.9 ± 1.19 (2)	
WEEK 7	65.1 ± 1.20 (6)	66.6 ± 1.61 (2)		77.1 ± 7.08 (2)		70.3 ± 3.16 (2)		63.4 ± .058 (2)	
WEEK 8	67.6 ± 1.59 (6)	65.6 ± 1.63 (2)		71.1 ± 3.70 (2)		66.9 ± 3.03 (2)		61.4 ± .251 (2)	
WEEK 9	59.7 ± 1.09 (4)	60.7 ± .463 (2)		70.9 ± 6.11 (2)		66.9 ± 2.57 (2)		63.2 ± .271 (2)	
WEEK 10	65.1 ± 2.35 (4)	63.5 ± 3.91 (2)		69.2 ± 1.71 (2)		70.3 ± 6.64 (2)		61.0 ± .287 (2)	
WEEK 11	63.5 ± .881 (4)	60.1 ± .517 (2)		64.4 ± 1.80 (2)		64.8 ± 3.57 (2)		60.7 ± 1.67 (2)	
WEEK 12	66.5 ± 2.77 (4)	62.9 ± 1.05 (2)		67.0 ± 3.64 (2)		64.9 ± 4.60 (2)		73.3 ± 9.44 (2)	
WEEK 13	69.0 ± 3.53 (4)	64.9 ± .320 (2)		72.8 ± 7.89 (2)		68.2 ± 4.96 (2)		61.5 ± .284 (2)	
WEEK 14	69.6 ± 1.48 (2)	65.5 ± 2.97 (2)		70.4 ± 9.28 (2)		76.2 ± 4.41 (2)		85.8 ± 3.39 (2)	
WEEK 15	55.9 ± 2.18 (2)	61.9 ± 1.69 (2)		75.6 ± 10.7 (2)		70.1 ± 3.55 (2)		75.9 ± .017 (2)	
WEEK 16	59.8 ± .509 (2)	66.0 ± 3.15 (2)		80.7 ± 17.6 (2)		74.1 ± 9.86 (2)		88.6 ± 6.72 (2)	
WEEK 17	77.0 ± 4.19 (2)	76.5 ± 7.06 (2)		76.6 ± 1.53 (2)		81.7 ± 9.09 (2)		82.8 ± 8.65 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 83

DOSES OF TNT (MG/KG (BODY WT)/DAY) IN DIETS CONSUMED BY MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS			
	.002 % IN DIET	.01 % IN DIET	.05 % IN DIET	.25 % IN DIET
WEEK 1	1.85	9.06	43.5	159.0
WEEK 2	1.89	9.59	46.6	210.3
WEEK 3	1.75	8.87	42.9	205.5
WEEK 4	1.57	7.75	37.7	186.8
WEEK 5	1.46	7.15	35.9	171.8
WEEK 6	1.41	6.58	34.9	161.1
WEEK 7	1.35	6.55	33.0	152.7
WEEK 8	1.19	6.26	30.8	144.4
WEEK 9	1.12	5.77	29.2	141.8
WEEK 10	1.16	6.02	29.7	140.5
WEEK 11	1.14	5.56	28.1	132.1
WEEK 12	1.15	5.61	25.8	139.1
WEEK 13	1.19	5.80	28.9	133.8

TABLE 84

DOSES OF TNT (MG/KG (BODY WT)/DAY) IN DIETS CONSUMED BY
FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS			
	.002 % IN DIET	.01 % IN DIET	.05 % IN DIET	.25 % IN DIET
WEEK 1	1.68	8.68	38.7	137.1
WEEK 2	1.79	9.14	44.9	208.4
WEEK 3	1.76	8.61	42.6	195.7
WEEK 4	1.57	7.64	38.8	180.2
WEEK 5	1.50	7.57	35.8	174.1
WEEK 6	1.42	7.44	37.1	159.3
WEEK 7	1.38	7.27	35.5	155.9
WEEK 8	1.33	6.71	33.9	151.5
WEEK 9	1.21	6.68	32.8	152.4
WEEK 10	1.32	6.57	34.9	151.0
WEEK 11	1.23	6.13	32.0	143.4
WEEK 12	1.29	6.70	31.9	162.6
WEEK 13	1.35	7.13	34.9	156.2

TABLE 85

EFFECTS OF TNT ON ORGAN WEIGHTS (C),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF HALF RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP		TREATMENT GROUPS .002 % IN DIET		T R	.01 % IN DIET		T R	.05 % IN DIET		T R	.25 % IN DIET		T R
FINAL WT (G)		323.80 ± 7.55	(5)	358.60 ± 9.91	(5)		335.20 ± 10.3	(5)		351.60 ± 2.32	(5)		311.60 ± 8.30	(5)	
BRAIN		2.15 ± .051	(5)	2.09 ± .053	(5)		2.02 ± .031	(5)		2.08 ± .047	(5)		1.97 ± .012	(5)	
HEART		1.23 ± .079	(5)	1.30 ± .047	(5)		1.19 ± .057	(5)		1.29 ± .051	(5)		1.19 ± .043	(5)	
KIDNEYS		3.04 ± .183	(5)	2.68 ± .092	(5)		2.93 ± .141	(5)		3.28 ± .060	(5)		2.67 ± .103	(5)	
LIVER		14.17 ± .543	(5)	15.03 ± .513	(5)		14.52 ± .594	(5)		16.46 ± .738	(5)		17.32 ± .537	(5)	*
SPLEEN		.73 ± .075	(5)	.77 ± .047	(5)		.90 ± .123	(5)		.89 ± .068	(5)		1.54 ± .064	(5)	+ D
TESTES		5.00 ± .132	(5)	4.38 ± .207	(5)		4.63 ± .162	(5)		4.59 ± .191	(5)		1.66 ± .222	(5)	+ D
BRAIN/BYWT		6.64 ± .232	(5)	5.83 ± .177	(5)		6.06 ± .215	(5)		5.92 ± .144	(5)		6.34 ± .153	(5)	
HEART/BYWT		3.81 ± .259	(5)	3.64 ± .104	(5)		3.54 ± .150	(5)		3.67 ± .160	(5)		3.83 ± .082	(5)	
KIDNEYS/BYWT	*	9.39 ± .488	(5)	7.46 ± .106	(5)	*	8.72 ± .183	(5)		9.32 ± .135	(5)		8.56 ± .254	(5)	
LIVER/BYWT		43.77 ± 1.32	(5)	41.92 ± .800	(5)		43.33 ± 1.31	(5)		46.85 ± 2.17	(5)		55.60 ± 1.27	(5)	+ A
SPLEEN/BYWT		2.25 ± .193	(5)	2.16 ± .167	(5)		2.70 ± .369	(5)		2.52 ± .184	(5)		4.93 ± .107	(5)	+ D
TESTES/BYWT		15.45 ± .386	(5)	12.22 ± .405	(5)	+ A	13.83 ± .290	(5)		13.05 ± .589	(5)	*	5.35 ± .701	(5)	+ D
HEART/BRAIN		.57 ± .023	(5)	.63 ± .027	(5)		.59 ± .030	(5)		.62 ± .017	(5)		.61 ± .019	(5)	
KIDNEYS/BRAIN		1.42 ± .072	(5)	1.28 ± .045	(5)		1.45 ± .072	(5)		1.58 ± .051	(5)		1.35 ± .052	(5)	
LIVER/BRAIN		6.61 ± .230	(5)	7.23 ± .320	(5)		7.18 ± .292	(5)		7.92 ± .317	(5)		8.78 ± .258	(5)	+ A
SPLEEN/BRAIN		.34 ± .033	(5)	.37 ± .021	(5)		.45 ± .068	(5)	B	.43 ± .029	(5)	B	.78 ± .033	(5)	+ D
TESTES/BRAIN		2.34 ± .105	(5)	2.10 ± .079	(5)		2.30 ± .095	(5)		2.20 ± .051	(5)		.84 ± .116	(5)	+ D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 86

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
FINAL WT (G)		229.00 ± 4.46 (5)	223.40 ± 6.93 (5)		213.80 ± 5.02 (5)		212.60 ± 8.43 (5)		184.80 ± 7.62 (5)	+ A
BRAIN		1.95 ± .022 (5)	1.88 ± .035 (5)		1.79 ± .023 (5)		1.91 ± .070 (5)		1.84 ± .035 (5)	
HEART		1.03 ± .033 (5)	.87 ± .040 (5)		.80 ± .057 (5)	A	1.02 ± .070 (5)		.90 ± .079 (5)	
KIDNEYS		1.97 ± .046 (5)	1.85 ± .062 (5)		1.69 ± .083 (5)		1.81 ± .101 (5)		1.71 ± .101 (5)	
LIVER		9.13 ± .302 (5)	8.87 ± .347 (5)		7.70 ± .448 (5)		9.35 ± .414 (5)		8.99 ± .438 (5)	
SPLEEN		.61 ± .040 (5)	.58 ± .040 (5)		.48 ± .042 (5)	B	.60 ± .042 (5)		1.07 ± .036 (5)	+ D
BRAIN/BYWT		8.54 ± .240 (5)	8.43 ± .171 (5)		8.40 ± .168 (5)		8.99 ± .349 (5)		9.99 ± .406 (5)	*
HEART/BYWT	*	4.51 ± .107 (5)	3.89 ± .071 (5)	*	3.73 ± .198 (5)	*	4.82 ± .4'5 (5)		4.89 ± .403 (5)	
KIDNEYS/BYWT		8.59 ± .192 (5)	8.29 ± .269 (5)		7.91 ± .256 (5)		8.53 ± .356 (5)		9.31 ± .576 (5)	
LIVER/BYWT		39.85 ± .954 (5)	39.74 ± 1.16 (5)		35.91 ± 1.34 (5)		44.01 ± 1.05 (5)		48.69 ± 1.58 (5)	+ A
SPLEEN/BYWT		2.67 ± .144 (5)	2.58 ± .133 (5)		2.23 ± .166 (5)		2.84 ± .237 (5)		5.83 ± .182 (5)	+ D
HEART/BRAIN		.53 ± .022 (5)	.46 ± .016 (5)	A	.45 ± .028 ( )	A	.54 ± .060 (5)		.49 ± .035 (5)	
KIDNEYS/BRAIN		1.01 ± .029 (5)	.98 ± .026 (5)		.94 ± .039 (5)		.96 ± .074 (5)		.93 ± .050 (5)	
LIVER/BRAIN		4.68 ± .190 (5)	4.71 ± .115 (5)		4.30 ± .251 (5)		4.92 ± .200 (5)		4.90 ± .248 (5)	
SPLEEN/BRAIN		.31 ± .023 (5)	.31 ± .016 (5)		.27 ± .020 (5)	A	.32 ± .021 (5)		.58 ± .014 (5)	+ D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 87

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
FINAL WT (G)		478.20 ± 22.4 (5)	450.60 ± 12.3 (5)		458.00 ± 10.6 (5)		446.00 ± 9.08 (5)		360.80 ± 15.1 (5)	+ A
BRAIN		2.16 ± .032 (5)	2.13 ± .042 (5)		2.22 ± .051 (5)		2.24 ± .020 (5)		2.10 ± .041 (5)	
HEART		1.61 ± .097 (5)	1.49 ± .051 (5)		1.60 ± .113 (5)		1.60 ± .052 (5)		1.28 ± .077 (5)	
KIDNEYS		3.78 ± .164 (5)	3.60 ± .262 (5)		3.45 ± .084 (5)		4.08 ± .130 (5)		2.92 ± .161 (5)	* A
LIVER		15.08 ± 1.16 (5)	13.82 ± .660 (5)		13.71 ± .872 (5)		15.58 ± .549 (5)		14.10 ± .976 (5)	
SPLEEN	+	.73 ± .038 (5)	.71 ± .036 (5)		.79 ± .053 (5)		.90 ± .034 (5)	*	1.95 ± .200 (5)	* D
TESTES	*	3.43 ± .101 (5)	3.48 ± .140 (5)		3.09 ± .405 (5)		3.51 ± .134 (5)		1.13 ± .071 (5)	+ D
BRAIN/BYWT		4.55 ± .198 (5)	4.75 ± .163 (5)		4.84 ± .060 (5)		5.03 ± .109 (5)		5.85 ± .195 (5)	+ A
HEART/BYWT		3.36 ± .170 (5)	3.32 ± .105 (5)		3.49 ± .203 (5)		3.59 ± .140 (5)		3.57 ± .223 (5)	
KIDNEYS/BYWT		7.93 ± .313 (5)	7.97 ± .492 (5)		7.54 ± .251 (5)		9.16 ± .355 (5)		8.11 ± .340 (5)	
LIVER/BYWT		31.41 ± 1.21 (5)	30.72 ± 1.47 (5)		29.94 ± 1.76 (5)		34.90 ± .669 (5)		38.93 ± .995 (5)	* A
SPLEEN/BYWT	+	1.53 ± .075 (5)	1.57 ± .074 (5)		1.73 ± .128 (5)		2.02 ± .074 (5)	+	5.40 ± .518 (5)	* D
TESTES/BYWT	*	7.26 ± .492 (5)	7.70 ± .114 (5)		6.74 ± .839 (5)		7.86 ± .169 (5)		3.17 ± .314 (5)	+ C
HEART/BRAIN		.74 ± .037 (5)	.70 ± .021 (5)		.72 ± .050 (5)		.72 ± .027 (5)		.61 ± .029 (5)	A
KIDNEYS/BRAIN		1.75 ± .078 (5)	1.68 ± .116 (5)		1.56 ± .063 (5)		1.82 ± .043 (5)		1.39 ± .063 (5)	A
LIVER/BRAIN		6.98 ± .531 (5)	6.48 ± .303 (5)		6.21 ± .429 (5)		6.96 ± .225 (5)		6.70 ± .352 (5)	
SPLEEN/BRAIN	+	.34 ± .013 (5)	.33 ± .015 (5)		.36 ± .028 (5)		.40 ± .015 (5)	*	.93 ± .097 (5)	* D
TESTES/BRAIN	*	1.59 ± .055 (5)	1.63 ± .076 (5)		1.40 ± .185 (5)		1.57 ± .061 (5)		.54 ± .037 (5)	+ D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 88

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
FINAL WT (G)		252.40 ± 4.27 (5)	263.20 ± 8.94 (5)		257.60 ± 11.9 (5)		233.60 ± 5.36 (5)		202.40 ± 8.67 (5)	+ A
BRAIN		1.92 ± .059 (5)	1.96 ± .038 (5)		2.05 ± .060 (5)		1.95 ± .048 (5)		1.96 ± .022 (5)	
HEART		.83 ± .036 (5)	.94 ± .031 (5)	A	1.00 ± .052 (5)	B	.87 ± .043 (5)		.91 ± .051 (5)	A
KIDNEYS		1.92 ± .038 (5)	1.99 ± .085 (5)		1.91 ± .118 (5)		1.95 ± .068 (5)		1.67 ± .109 (5)	
LIVER		6.98 ± .239 (5)	7.27 ± .472 (5)		6.35 ± .689 (5)		6.98 ± .235 (5)		7.53 ± .576 (5)	
SPLEEN	+	.47 ± .026 (5)	.58 ± .029 (5)	*	.58 ± .046 (5)		.56 ± .040 (5)		1.39 ± .177 (5)	* D
BRAIN/BYWT		7.62 ± .276 (5)	7.48 ± .247 (5)		8.01 ± .402 (5)		8.35 ± .290 (5)		9.75 ± .442 (5)	+ A
HEART/BYWT		3.37 ± .120 (5)	3.57 ± .066 (5)		3.89 ± .211 (5)		3.72 ± .153 (5)		4.51 ± .190 (5)	+ B
KIDNEYS/BYWT		7.61 ± .238 (5)	7.57 ± .103 (5)		7.41 ± .228 (5)		8.37 ± .299 (5)		8.25 ± .284 (5)	
LIVER/BYWT		27.68 ± .923 (5)	27.52 ± .901 (5)		24.48 ± 1.86 (5)		29.87 ± .589 (5)		37.01 ± 1.52 (5)	+ A
SPLEEN/BYWT	*	1.87 ± .118 (5)	2.24 ± .167 (5)		2.26 ± .216 (5)		2.39 ± .186 (5)		6.83 ± .730 (5)	* D
HEART/BRAIN		.43 ± .018 (5)	.48 ± .016 (5)	A	.49 ± .013 (5)	A	.45 ± .031 (5)		.47 ± .023 (5)	
KIDNEYS/BRAIN		1.00 ± .021 (5)	1.02 ± .036 (5)		.94 ± .056 (5)		1.01 ± .049 (5)		.85 ± .055 (5)	
LIVER/BRAIN		3.65 ± .161 (5)	3.71 ± .227 (5)		3.09 ± .292 (5)		3.59 ± .107 (5)		3.84 ± .289 (5)	
SPLEEN/BRAIN	+	.25 ± .011 (5)	.30 ± .015 (5)	*	.28 ± .026 (5)		.28 ± .016 (5)		.71 ± .092 (5)	* D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 89

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE RATS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
FINAL WT (G)		417.60 ± 14.4 (5)	408.00 ± 15.3 (5)		389.80 ± 11.0 (5)		391.80 ± 6.89 (5)		378.80 ± 7.78 (5)	
BRAIN		2.12 ± .041 (5)	2.20 ± .030 (5)		2.17 ± .053 (5)		2.15 ± .047 (5)		2.16 ± .039 (5)	
HEART		1.58 ± .060 (5)	1.61 ± .034 (5)		1.42 ± .049 (5)		1.33 ± .036 (5)		1.46 ± .059 (5)	
KIDNEYS		3.31 ± .078 (5)	3.39 ± .234 (5)		3.30 ± .183 (5)		3.19 ± .096 (5)		3.05 ± .107 (5)	
LIVER		16.91 ± .963 (5)	13.04 ± .765 (5)	* A	14.62 ± .953 (5)		11.98 ± .309 (5)	+ A	11.94 ± .392 (5)	+ A
SPLEEN		.77 ± .049 (5)	.78 ± .057 (5)		.78 ± .046 (5)		.75 ± .069 (5)		.78 ± .037 (5)	
TESTES	+	3.34 ± .353 (5)	3.28 ± .019 (5)		3.31 ± .216 (5)		3.38 ± .053 (5)		1.57 ± .076 (5)	* C
BRAIN/BYWT		5.10 ± .208 (5)	5.42 ± .220 (5)		5.56 ± .089 (5)		5.50 ± .199 (5)		5.72 ± .187 (5)	
HEART/BYWT		3.52 ± .131 (5)	3.98 ± .158 (5)		3.66 ± .182 (5)		3.40 ± .090 (5)		3.85 ± .239 (5)	
KIDNEYS/BYWT		7.96 ± .231 (5)	8.27 ± .289 (5)		8.53 ± .680 (5)		8.17 ± .348 (5)		8.04 ± .176 (5)	
LIVER/BYWT	*	40.39 ± 1.10 (5)	31.91 ± 1.02 (5)	+ A	37.63 ± 2.62 (5)		30.58 ± .412 (5)	+ A	31.50 ± .525 (5)	+ A
SPLEEN/BYWT		1.85 ± .094 (5)	1.91 ± .100 (5)		2.00 ± .114 (5)		1.92 ± .191 (5)		2.06 ± .124 (5)	
TESTES/BYWT	*	9.21 ± .817 (5)	8.08 ± .309 (5)		8.55 ± .740 (5)		8.63 ± .229 (5)		4.14 ± .145 (5)	* C
HEART/BRAIN		.55 ± .034 (5)	.73 ± .007 (5)	A	.66 ± .030 (5)		.62 ± .024 (5)		.67 ± .035 (5)	
KIDNEYS/BRAIN		1.57 ± .048 (5)	1.54 ± .099 (5)		1.53 ± .109 (5)		1.49 ± .055 (5)		1.41 ± .073 (5)	
LIVER/BRAIN		8.00 ± .494 (5)	5.92 ± .312 (5)	* A	6.78 ± .518 (5)		5.59 ± .255 (5)	+ A	5.54 ± .224 (5)	+ A
SPLEEN/BRAIN		.37 ± .027 (5)	.35 ± .023 (5)		.36 ± .025 (5)		.35 ± .026 (5)		.36 ± .016 (5)	
TESTES/BRAIN	+	1.82 ± .184 (5)	1.49 ± .024 (5)		1.53 ± .117 (5)		1.57 ± .023 (5)		.73 ± .043 (5)	* C

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 90

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE RATS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
FINAL WT (G)		231.60 ± 4.41 (5)	227.20 ± 6.41 (5)		234.40 ± 9.39 (5)		229.60 ± 6.82 (5)		209.80 ± 5.21 (5)	
BRAIN	+	1.92 ± .030 (5)	2.01 ± .060 (5)		2.04 ± .028 (5)	+	2.18 ± .178 (5)		1.97 ± .C29 (5)	
HEART		.85 ± .056 (5)	1.01 ± .078 (5)		.90 ± .078 (5)		.90 ± .053 (5)		.84 ± .036 (5)	
KIDNEYS		1.75 ± .067 (5)	1.84 ± .041 (5)		1.81 ± .086 (5)		1.76 ± .050 (5)		1.75 ± .090 (5)	
LIVER		7.76 ± .530 (5)	6.57 ± .424 (5)		6.39 ± .289 (5)		6.45 ± .136 (5)		6.76 ± .491 (5)	
SPLEEN		.58 ± .035 (5)	.62 ± .041 (5)		.54 ± .036 (5)		.56 ± .027 (5)		.60 ± .042 (5)	
BRAIN/BYWT		8.29 ± .265 (5)	8.87 ± .305 (5)		8.77 ± .383 (5)		9.52 ± .714 (5)		9.42 ± .160 (5)	
HEART/BYWT		3.70 ± .291 (5)	4.43 ± .289 (5)		3.82 ± .299 (5)		3.90 ± .159 (5)		4.02 ± .152 (5)	
KIDNEYS/BYWT	*	7.58 ± .283 (5)	8.13 ± .179 (5)		7.76 ± .384 (5)		7.66 ± .046 (5)		8.32 ± .224 (5)	
LIVER/BYWT		33.41 ± 1.77 (5)	28.91 ± 1.71 (5)		27.29 ± 1.00 (5)		28.15 ± .502 (5)		32.20 ± 2.09 (5)	
SPLEEN/BYWT		2.50 ± .187 (5)	2.71 ± .176 (5)		2.31 ± .087 (5)		2.46 ± .133 (5)		2.86 ± .158 (5)	
HEART/BRAIN		.44 ± .023 (5)	.50 ± .035 (5)	A	.44 ± .041 (5)		.42 ± .032 (5)		.43 ± .015 (5)	
KIDNEYS/BRAIN		.92 ± .037 (5)	.92 ± .041 (5)		.89 ± .035 (5)		.82 ± .050 (5)	A	.89 ± .036 (5)	
LIVER/BRAIN		4.06 ± .312 (5)	3.29 ± .257 (5)		3.13 ± .137 (5)		3.02 ± .207 (5)	A	3.42 ± .226 (5)	
SPLEEN/BRAIN		.30 ± .017 (5)	.31 ± .028 (5)		.27 ± .019 (5)	A	.26 ± .010 (5)	A	.3C ± .019 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D, RATIO TEST CANNOT BE CALCULATED - * .

TABLE 91

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE RATS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

			TREATMENT GROUPS							
DEPENDENT VARIABLE	B C	CONTROL GROUP	.002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
FINAL WT (G)		520.20 ± 15.0 (5)	482.[illegible]0 ± 23.1 (5)		504.00 ± 13.3 (5)		513.60 ± 23.7 (5)		435.20 ± 15.4 (5)	
BRAIN	*	2.25 ± .079 (5)	2.26+ ± .022 (5)		2.38 ± .030 (5)		2.38 ± .022 (5)		2.41 ± .078 (5)	
HEART		1.78 ± .070 (5)	1.74 ± .078 (5)		1.77 ± .155 (5)		1.67 ± .046 (5)		1.55 ± .060 (5)	
KIDNEYS		4.10 ± .107 (5)	3.59 ± .270 (5)		3.93 ± .185 (5)		4.15 ± .108 (5)		3.21 ± .057 (5)	* A
LIVER		16.52 ± 1.07 (5)	14.05 ± 1.36 (5)		14.74 ± 1.13 (5)		14.91 ± .760 (5)		13.31 ± .915 (5)	
SPLEEN		.93 ± .064 (5)	.87 ± .068 (5)		.77 ± .046 (5)		.90 ± .019 (5)		1.07 ± .067 (5)	
TESTES		3.64 ± .304 (5)	3.58 ± .171 (5)		3.32 ± .077 (5)		3.78 ± .346 (5)		1.57 ± .139 (5)	+ C
BRAIN/BYWT		4.35 ± .221 (5)	4.72 ± .238 (5)		4.74 ± .103 (5)		4.67 ± .223 (5)		5.62 ± .434 (4)	*
HEART/BYWT		3.44 ± .212 (5)	3.63 ± .247 (5)		3.49 ± .247 (5)		3.27 ± .187 (5)		3.56 ± .159 (4)	
KIDNEYS/BYWT		7.89 ± .247 (5)	7.42 ± .379 (5)		7.78 ± .212 (5)		8.18 ± .562 (5)		7.47 ± .354 (4)	
LIVER/BYWT		31.79 ± 1.34 (5)	26.87 ± 1.49 (5)		29.17 ± 1.71 (5)		29.06 ± .861 (5)		30.77 ± 1.35 (4)	
SPLEEN/BYWT		1.79 ± .105 (5)	1.80 ± .111 (5)		1.53 ± .097 (5)		1.77 ± .093 (5)		2.52 ± .104 (4)	+ A
TESTES/BYWT	*	7.02 ± .603 (5)	7.43 ± .160 (5)		6.61 ± .221 (5)		7.52 ± .989 (5)		3.63 ± .383 (4)	* B
HEART/BRAIN		.79 ± .025 (5)	.77 ± .028 (5)		.74 ± .060 (5)		.70 ± .015 (5)	A	.64 ± .022 (5)	A
KIDNEYS/BRAIN		1.82 ± .073 (5)	1.59 ± .123 (5)		1.65 ± .072 (5)		1.75 ± .054 (5)		1.33 ± .030 (5)	+ A
LIVER/BRAIN		7.43 ± .692 (5)	6.22 ± .605 (5)		6.18 ± .426 (5)		6.28 ± .351 (5)		5.55 ± .441 (5)	
SPLEEN/BRAIN		.41 ± .025 (5)	.39 ± .029 (5)		.32 ± .019 (5)	B	.38 ± .011 (5)		.45 ± .034 (5)	
TESTES/BRAIN		1.62 ± .127 (5)	1.59 ± .076 (5)		1.39 ± .029 (5)		1.59 ± .142 (5)		.65 ± .063 (5)	+ C

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 92

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE RATS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T	R	.01 % IN DIET	T	R	.05 % IN DIET	T	R	.25 % IN DIET	T	R
FINAL WT (G)		271.60 ± 4.11 (5)	259.00 ± 10.7 (5)			268.80 ± 11.4 (5)			254.60 ± 7.59 (5)			238.00 ± 10.5 (5)		
BRAIN		2.07 ± .046 (5)	2.09 ± .060 (5)			2.01 ± .030 (5)			2.11 ± .030 (5)			2.37 ± .103 (5)	*	
HEART		1.15 ± .100 (5)	1.00 ± .044 (5)			1.11 ± .056 (5)			1.02 ± .052 (5)			1.45 ± .119 (5)		
KIDNEYS	+	2.10 ± .059 (5)	1.95 ± .060 (5)			2.07 ± .111 (5)			2.17 ± .076 (5)			2.92 ± .337 (5)		
LIVER	+	7.16 ± .099 (5)	7.09 ± .398 (5)			7.11 ± .330 (5)			7.11 ± .250 (5)			12.16 ± 1.65 (5)	*	
SPLEEN	+	.58 ± .030 (5)	.56 ± .044 (5)			.62 ± .032 (5)			.55 ± .012 (5)			1.01 ± .113 (5)	*	A
BRAIN/BYWT		7.65 ± .275 (5)	8.15 ± .483 (5)			7.54 ± .324 (5)			8.31 ± .321 (5)			10.04 ± .771 (4)	*	A
HEART/BYWT		4.22 ± .330 (5)	3.87 ± .178 (5)			4.20 ± .350 (5)			3.99 ± .115 (5)			6.38 ± .407 (4)	+	B
KIDNEYS/BYWT		7.74 ± .248 (5)	7.56 ± .369 (5)			7.72 ± .459 (5)			8.52 ± .254 (5)			13.35 ± .673 (4)	+	D
LIVER/BYWT	+	26.36 ± .106 (5)	27.48 ± 1.67 (5)			26.45 ± .737 (5)			27.93 ± .435 (5)	*		55.27 ± 4.20 (4)	*	D
SPLEEN/BYWT		2.12 ± .098 (5)	2.18 ± .184 (5)			2.32 ± .106 (5)			2.15 ± .073 (5)			4.51 ± .283 (4)	+	D
HEART/BRAIN		.56 ± .050 (5)	.48 ± .018 (5)		A	.55 ± .034 (5)			.48 ± .027 (5)		A	.61 ± .036 (5)		A
KIDNEYS/BRAIN	*	1.01 ± .023 (5)	.93 ± .043 (5)			1.02 ± .042 (5)			1.03 ± .047 (5)			1.22 ± .119 (5)		
LIVER/BRAIN	*	3.46 ± .113 (5)	3.40 ± .211 (5)			3.53 ± .146 (5)			3.38 ± .158 (5)			5.11 ± .657 (5)		
SPLEEN/BRAIN	*	.28 ± .015 (5)	.27 ± .026 (5)			.31 ± .015 (5)			.26 ± .008 (5)			.43 ± .046 (5)	*	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 93

EFFECTS OF TNT ON HEMATOLOGY
OF MALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
RBC (X 10^6)	*	6.72 ± .115 (3)	7.20 ± .121 (5)	*	7.34 ± .196 (5)	*	7.09 ± .091 (5)		5.80 ± .439 (4)	
HGB (G %)	*	13.40 ± .200 (3)	14.08 ± .299 (5)		14.10 ± .224 (5)		13.38 ± .116 (5)		12.00 ± .802 (4)	
HCT (%)	+	39.07 ± .088 (3)	40.56 ± .928 (5)		39.84 ± .716 (5)		38.26 ± .244 (5)	*	35.80 ± 2.29 (4)	
MCV (U)^3		57.67 ± .882 (3)	56.40 ± 1.44 (5)		54.40 ± .678 (5)		54.00 ± .447 (5)		61.50 ± 1.19 (4)	
MCH (UUG)		19.97 ± .273 (3)	19.64 ± .481 (5)		19.30 ± .230 (5)		18.96 ± .240 (5)		20.85 ± .380 (4)	
MCHC (%)		34.40 ± .557 (3)	34.86 ± .103 (5)		35.52 ± .165 (5)		35.06 ± .150 (5)		33.72 ± .189 (4)	
WBC (X 10^3)	*	8.63 ± 2.09 (3)	8.00 ± 1.01 (5)	•	7.16 ± 1.41 (5)	•	8.82 ± 1.32 (5)	•	21.85 ± 5.00 (4)	
PMN (%)		17.00 ± 4.04 (3)	16.80 ± 2.35 (5)		16.40 ± 3.36 (5)		13.80 ± 1.24 (5)		15.20 ± 2.01 (5)	
BANDS (%)		1.00 ± .577 (3)	.60 ± .400 (5)	•	.60 ± .400 (5)	•	0.00 ± 0.00 (5)	•	1.80 ± .916 (5)	•
LYMPH (%)		80.33 ± 3.53 (3)	81.00 ± 2.81 (5)		81.20 ± 3.60 (5)		84.60 ± 1.47 (5)		81.40 ± 1.78 (5)	
MONO (%)		1.00 ± .577 (3)	.60 ± .400 (5)	•	1.60 ± .678 (5)	•	1.20 ± .735 (5)	•	1.00 ± .548 (5)	•
EOSIN (%)		.67 ± .333 (3)	1.00 ± .447 (5)	•	.20 ± .200 (5)	•	.40 ± .400 (5)	•	.60 ± .245 (5)	•
BASO (%)		0.00 ± 0.00 (3)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 94

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
			TREATMENT GROUPS							
RBC (X 10^6)		5.82 ± .321 (5)	7.40 ± .134 (5)		7.68 ± .154 (5)		6.90 ± .174 (5)		5.69 ± .158 (4)	
HGB (G %)		13.02 ± .545 (5)	13.82 ± .193 (5)		14.12 ± .376 (5)		12.84 ± .320 (5)		11.23 ± .330 (4)	
HCT (%)		3[illegible].78 ± 1.69 (5)	40.74 ± .478 (5)		41.44 ± .915 (5)		38.[illegible]8 ± .739 (5)		34.20 ± .892 (4)	
MCV (U)3		56.50 ± .200 (5)	55.00 ± .633 (5)		54.00 ± .548 (5)		55.[illegible]0 ± .735 (5)		59.75 ± 1.25 (4)	
MCH (UUG)		19.18 ± .139 (5)	18.70 ± .192 (5)		18.44 ± .27[illegible] (5)		18.68 ± .242 (5)		19.83 ± .357 (4)	
MCHC (%)		33.74 ± .240 (5)	33.98 ± .107 (5)		34.18 ± .201 (5)		33.68 ± .153 (5)		33.05 ± .132 (4)	
WBC (X 10^3)		9.22 ± 1.56 (5)	6.76 ± 1.89 (5)		9.34 ± .770 (5)		9.06 ± .863 (5)		8.55 ± .953 (4)	
PMN (%)		10.60 ± 1.12 (5)	16.80 ± 2.58 (5)		13.20 ± 1.46 (5)		13.60 ± 1.72 (5)		14.40 ± 2.11 (5)	
BANDS (%)		.20 ± .200 (5)	1.60 ± .600 (5)	•	.20 ± .200 (5)	•	1.40 ± .678 (5)	•	0.00 ± 0.00 (5)	•
LYMPH (%)		87.00 ± 1.52 (5)	78.00 ± 3.05 (5)		84.80 ± 1.62 (5)		82.80 ± 2.29 (5)		84.60 ± 2.11 (5)	
MONO (%)		2.00 ± .837 (5)	2.00 ± .548 (5)		1.00 ± .447 (5)		1.20 ± .800 (5)		.20 ± .200 (5)	B
EOSIN (%)		.20 ± .200 (5)	1.60 ± .510 (5)	•	.80 ± .374 (5)	•	1.00 ± .316 (5)	•	.80 ± .200 (5)	•
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - L. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 95

FFFFCTS OF TNT ON HEMATOLOGY
OF MALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
RBC (X 10^6)		8.48 ± .080 (5)	8.57 ± .125 (5)		8.30 ± .076 (5)		7.92 ± .130 (5)		6.21 ± .194 (5)	
HGB (G %)		14.88 ± .183 (5)	15.33 ± .281 (5)		14.88 ± .186 (5)		13.54 ± .304 (5)	*	12.66 ± .129 (5)	+ A
HCT (%)		42.02 ± .334 (5)	43.22 ± .673 (5)		41.68 ± .465 (5)		38.32 ± .831 (5)	+	36.94 ± .442 (5)	+
MCV $(U)^3$	+	49.00 ± .548 (5)	50.00 ± .316 (5)		49.60 ± .245 (5)		48.00 ± .633 (5)		58.40 ± 1.81 (5)	
MCH (UUG)	*	17.44 ± .248 (5)	17.70 ± .114 (5)		17.78 ± .107 (5)		17.00 ± .261 (5)		20.34 ± .568 (5)	*
MCHC (%)		35.38 ± .188 (5)	35.34 ± .178 (5)		35.70 ± .089 (5)		35.40 ± .141 (5)		34.34 ± .172 (5)	+
WBC (X 10^3)		7.40 ± .638 (5)	10.70 ± 1.25 (5)		10.66 ± 1.32 (5)		9.48 ± 1.01 (5)		13.46 ± 1.01 (5)	
PMN (%)		12.20 ± 1.16 (5)	11.40 ± 2.14 (5)		15.00 ± 4.16 (5)		12.80 ± 1.80 (5)		7.80 ± 1.36 (5)	
BANDS (%)		1.40 ± .600 (5)	1.00 ± .316 (5)		.20 ± .200 (5)	B	.80 ± .374 (5)		1.80 ± .374 (5)	
LYMPH (%)		84.20 ± 1.71 (5)	86.60 ± 2.71 (5)		82.40 ± 4.35 (5)		85.20 ± 1.98 (5)		90.00 ± 1.38 (5)	
MONO (%)		1.20 ± .374 (5)	.80 ± .374 (5)		1.40 ± .510 (5)		.60 ± .245 (5)		.20 ± .200 (5)	B
EOSIN (%)		1.00 ± .316 (5)	.20 ± .200 (5)	B	1.00 ± .316 (5)		.60 ± .245 (5)		.20 ± .200 (5)	B
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 96

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
RBC (X 10^6)	*	7.71 ± .043 (5)	7.36 ± .280 (5)		7.61 ± .127 (5)		7.26 ± .099 (5)	*	5.48 ± .203 (5)	
HGB (G %)	*	14.82 ± .177 (5)	14.48 ± .685 (5)		14.04 ± .150 (5)	*	13.64 ± .252 (5)	*	11.72 ± .285 (5)	+ A
HCT (%)	*	43.30 ± .497 (5)	41.36 ± 1.88 (5)		40.62 ± .529 (5)	*	39.52 ± .700 (5)	*	34.60 ± .817 (5)	+ A
MCV $(U)^3$		55.20 ± .663 (5)	55.40 ± .678 (5)		52.60 ± .748 (5)		53.60 ± .812 (5)		62.00 ± 1.64 (5)	
MCH (UUG)		19.06 ± .202 (5)	19.50 ± .268 (5)		18.36 ± .211 (5)		18.66 ± .280 (5)		21.30 ± .680 (5)	+
MCHC (%)		34.14 ± .157 (5)	34.98 ± .107 (5)		34.60 ± .253 (5)		34.54 ± .137 (5)		33.86 ± .201 (5)	
WBC (X 10^3)	*	7.72 ± .567 (5)	7.54 ± .881 (5)		5.30 ± .492 (5)	*	7.76 ± .700 (5)		17.42 ± 2.37 (5)	
PMN (%)		16.40 ± 1.81 (5)	16.00 ± 1.92 (5)		16.60 ± 3.97 (5)		11.40 ± 2.16 (5)		7.80 ± 1.59 (5)	A
BANDS (%)		1.00 ± .447 (5)	.20 ± .200 (5)		2.00 ± .548 (5)		1.00 ± .548 (5)		.20 ± .200 (5)	
LYMPH (%)		81.00 ± 2.17 (5)	81.40 ± 2.52 (5)		80.40 ± 4.55 (5)		85.60 ± 1.36 (5)		90.60 ± 1.60 (5)	
MONO (%)		.80 ± .200 (5)	.80 ± .583 (5)		.60 ± .245 (5)		.80 ± .374 (5)		.40 ± .245 (5)	
EOSIN (%)	*	.80 ± .374 (5)	2.40 ± 1.08 (5)	•	.40 ± .245 (5)	•	1.20 ± .490 (5)	•	1.00 ± .316 (5)	•
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 97

EFFECTS OF TNT ON HEMATOLOGY
OF MALE RATS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	.002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
			TREATMENT GROUPS							
RBC (X 10^6)		7.92 ± .112 (5)	7.96 ± .197 (5)		8.32 ± .107 (5)		8.20 ± .067 (5)		8.21 ± .131 (5)	
HGB (G %)		14.76 ± .121 (5)	14.94 ± .387 (5)		15.50 ± .118 (5)		15.16 ± .157 (5)		15.26 ± .211 (5)	
HCT (%)		41.14 ± .328 (5)	41.14 ± 1.02 (5)		42.06 ± .378 (5)		42.94 ± .595 (5)		42.92 ± .600 (5)	
MCV $(U)^3$		52.00 ± .633 (5)	51.40 ± .812 (5)		50.60 ± .927 (5)		52.40 ± .812 (5)		52.20 ± .374 (5)	
MCH (UUG)		18.46 ± .181 (5)	19.02 ± .404 (5)		18.82 ± .275 (5)		18.42 ± .193 (5)		18.52 ± .086 (5)	
MCHC (%)		35.60 ± .173 (5)	36.18 ± .208 (5)		36.70 ± .130 (5)	+	35.36 ± .209 (5)		35.58 ± .116 (5)	
WBC (X 10^3)		9.26 ± 1.30 (5)	11.18 ± 1.81 (5)		10.00 ± 1.34 (5)		12.76 ± 2.41 (5)		8.82 ± 1.75 (5)	
PMN (%)		11.40 ± 2.29 (5)	13.40 ± 2.25 (5)		14.20 ± 2.35 (5)		12.60 ± 2.87 (5)		14.80 ± 2.97 (5)	
BANDS (%)		1.20 ± .374 (5)	.40 ± .245 (5)		2.40 ± .400 (5)		1.40 ± .748 (5)		.40 ± .245 (5)	
LYMPH (%)		86.00 ± 2.43 (5)	85.40 ± 1.99 (5)		82.40 ± 1.96 (5)		83.60 ± 2.94 (5)		83.60 ± 2.69 (5)	
M[illegible] (%)		.20 ± .200 (5)	0.00 ± 0.00 (5)	•	.20 ± .200 (5)	•	1.00 ± .548 (5)	•	.80 ± .490 (5)	•
[illegible] (%)		1.20 ± .490 (5)	.80 ± .374 (5)		.80 ± .583 (5)		1.40 ± .400 (5)		.40 ± .245 (5)	
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 98

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE RATS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T	R	.01 % IN DIET	T	R	.05 % IN DIET	T	R	.25 % IN DIET	T	R
RBC (X 10^6)		7.51 ± .114 (5)	7.73 ± .208 (5)			7.88 ± .221 (5)			7.39 ± .178 (5)			8.09 ± .120 (4)		
HGB (G %)		14.14 ± .316 (5)	15.10 ± .295 (5)			14.90 ± .382 (5)			14.06 ± .271 (5)			16.23 ± .266 (4)	+	
HCT (%)		39.04 ± 1.83 (5)	42.50 ± .828 (5)			43.64 ± 1.24 (5)			41.14 ± .721 (5)			45.33 ± .692 (4)	*	
MCV $(U)^3$		54.00 ± .447 (5)	54.40 ± .510 (5)			54.60 ± .510 (5)			55.60 ± .678 (5)			56.00 ± .408 (4)		
MCH (UUG)		18.82 ± .213 (5)	19.76 ± .191 (5)			18.92 ± .222 (5)			19.00 ± .212 (5)			19.98 ± .103 (4)	*	
MCHC (%)	*	34.38 ± .613 (5)	35.52 ± .120 (5)			34.36 ± .244 (5)			34.22 ± .208 (5)			35.85 ± .444 (4)		
WBC (X 10^3)		7.94 ± .803 (5)	8.76 ± 1.19 (5)			8.58 ± .795 (5)			6.38 ± .962 (5)			8.48 ± 1.31 (4)		
PMN (%)		10.00 ± 2.28 (5)	13.60 ± 2.60 (5)			10.20 ± 2.11 (5)			14.20 ± 3.25 (5)			11.00 ± 2.35 (4)		
BANDS (%)		1.60 ± .600 (5)	.40 ± .245 (5)		B	.20 ± .200 (5)		C	.20 ± .200 (5)		C	.50 ± .289 (4)		A
LYMPH (%)		87.40 ± 2.71 (5)	83.60 ± 2.62 (5)			87.00 ± 2.39 (5)			83.40 ± 3.82 (5)			88.50 ± 2.60 (4)		
MONO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		•	1.60 ± .678 (5)		•	.60 ± .400 (5)		•	0.00 ± 0.00 (4)		
EOSIN (%)		1.00 ± .633 (5)	2.40 ± .600 (5)		•	1.00 ± .775 (5)		•	1.60 ± .812 (5)		•	0.00 ± 0.00 (4)		•
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)			0.00 ± 0.00 (5)			0.00 ± 0.00 (5)			0.00 ± 0.00 (4)		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 99

EFFECTS OF TNT ON HEMATOLOGY
OF MALE RATS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
RBC (X 10^6)		8.28 ± .080 (5)	8.65 ± .204 (5)		8.43 ± .207 (5)		8.72 ± .060 (5)		8.50 ± .192 (4)	
HGB (G %)		14.52 ± .180 (5)	14.80 ± .187 (5)		14.94 ± .286 (5)		15.60 ± .200 (5)		16.10 ± .474 (4)	*
HCT (%)		40.92 ± .595 (5)	41.96 ± .541 (5)		41.80 ± .858 (5)		43.64 ± .447 (5)		48.37 ± .981 (4)	+ A
MCV (U)3		49.00 ± .894 (5)	48.00 ± .548 (5)		48.80 ± .800 (5)		49.60 ± .400 (5)		56.00 ± .408 (4)	
MCH (UUG)		17.26 ± .273 (5)	16.90 ± .207 (5)		17.54 ± .204 (5)		17.76 ± .206 (5)		18.73 ± .350 (4)	*
MCHC (%)		35.34 ± .325 (5)	35.12 ± .278 (5)		35.56 ± .273 (5)		35.56 ± .202 (5)		33.30 ± .394 (4)	+
WBC (X 10^3)		8.32 ± 1.29 (5)	11.00 ± 1.42 (5)		8.20 ± 1.33 (5)		11.10 ± 1.81 (5)		13.02 ± 1.53 (4)	
PMN (%)	*	19.00 ± 1.26 (5)	18.20 ± 4.33 (5)		17.40 ± 1.96 (5)		20.00 ± 1.84 (5)		36.00 ± 7.52 (5)	
BANDS (%)		.60 ± .400 (5)	0.00 ± 0.00 (5)	•	0.00 ± 0.00 (5)	•	1.00 ± 1.00 (5)	•	0.00 ± 0.00 (5)	•
LYMPH (%)	+	77.40 ± .400 (5)	78.60 ± 3.59 (5)		78.60 ± 2.79 (5)		75.00 ± 1.87 (5)		60.60 ± 8.19 (5)	
MONO (%)		2.60 ± 1.44 (5)	3.00 ± 1.14 (5)		3.00 ± .447 (5)		3.60 ± 1.44 (5)		3.20 ± .860 (5)	
EOSIN (%)		.40 ± .245 (5)	.20 ± .200 (5)	•	1.00 ± .633 (5)	•	.40 ± .245 (5)	•	.20 ± .200 (5)	•
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
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R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 100

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE RATS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
RBC (X 10⁶)	+	7.94 ± .110 (4)	7.84 ± .104 (4)		7.68 ± .152 (5)		8.18 ± .211 (5)		6.83 ± .869 (4)	
HGB (G %)	+	14.50 ± .238 (4)	14.65 ± .132 (4)		14.56 ± .298 (5)		14.75 ± .194 (4)		13.80 ± 1.83 (4)	
HCT (%)	+	41.40 ± .720 (4)	41.80 ± .392 (4)		41.84 ± .722 (5)		41.74 ± .516 (5)		41.33 ± 5.27 (4)	
MCV (U)3		51.75 ± 1.03 (4)	52.75 ± .947 (4)		53.80 ± .200 (5)		50.80 ± 1.07 (5)		59.00 ± .913 (4)	
MCH (UUG)	+	14.36 ± 3.63 (5)	14.72 ± 3.71 (5)		18.82 ± .165 (5)		18.15 ± .287 (4)		20.02 ± .253 (4)	
MCHC (%)		34.80 ± .255 (4)	34.92 ± .427 (4)		34.62 ± .153 (5)		35.15 ± .386 (4)		33.50 ± .204 (4)	
WBC (X 10³)		5.20 ± .626 (4)	6.20 ± .460 (4)		5.98 ± .275 (5)		7.34 ± .596 (5)		6.13 ± 1.06 (4)	
PMN (%)		17.50 ± 4.48 (4)	16.40 ± 1.94 (5)		25.60 ± 5.56 (5)		13.80 ± 2.03 (5)		20.75 ± 3.33 (4)	
BANDS (%)		1.67 ± 1.20 (3)	0.00 ± 0.00 (5)	D	.40 ± .245 (5)	B	0.00 ± 0.00 (5)	D	0.00 ± 0.00 (4)	D
LYMPH (%)		81.00 ± 4.78 (4)	81.80 ± 2.58 (5)		70.60 ± 5.22 (5)		83.20 ± 2.67 (5)		76.25 ± 4.07 (4)	
MONO (%)		0.00 ± 0.00 (5)	1.60 ± .678 (5)	*	2.20 ± .800 (5)	*	2.40 ± .678 (5)	*	2.50 ± 1.04 (4)	
EOSIN (%)		.20 ± .200 (5)	.20 ± .200 (5)	*	1.20 ± .490 (5)	*	.60 ± .245 (5)	*	.50 ± .289 (4)	*
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (4)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLF 101

EFFFCTS OF TNT ON CLINICAL CHFMISTRY
OF MALF RATS AFTER 4 WEEKS OF TREATMFNT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIFT	T	R	.01 % IN DIET	T	R	.05 % IN DIET	T	R	.25 % IN DIET	T	R
GLUCOSE (MG %)		180.50 ± 19.6 (4)	154.00 ± 8.11 (5)			152.40 ± 5.78 (5)			163.75 ± 6.79 (4)			160.00 ± 9.88 (5)		
BUN (MG %)		12.50 ± .645 (4)	18.6C ± .980 (5)	*	A	16.00 ± 1.00 (5)			18.50 ± .957 (4)	*	A	22.00 ± 1.38 (5)	+	C
CREAT (MG %)		.70 ± .168 (4)	.42 ± .056 (5)		A	.54 ± .024 (5)			.52 ± .048 (4)			.60 ± 0.00 (5)		
URIC ACID (MG)		2.17 ± .511 (4)	1.36 ± .147 (5)		A	1.32 ± .168 (5)		A	1.35 ± .132 (4)			1.68 ± .139 (5)		
NA (MEQ/L)		145.50 ± 2.06 (4)	144.20 ± .735 (5)			142.60 ± .510 (5)			141.25 ± 1.18 (4)			141.60 ± .980 (5)		
K (MEQ/L)	+	5.20 ± .838 (4)	5.06 ± .081 (5)			5.08 ± .116 (5)			5.18 ± .118 (4)			5.14 ± .218 (5)		
CO_2 (MEQ/L)	*	26.25 ± .250 (4)	27.20 ± .583 (5)			28.80 ± .374 (5)	+		28.50 ± .957 (4)			26.80 ± 1.43 (5)		
CL (MEQ/L)		103.25 ± 1.03 (4)	100.20 ± .663 (5)			99.60 ± .510 (5)			98.75 ± 1.03 (4)			97.60 ± 1.44 (5)	*	
CA (MG %)		9.75 ± .250 (4)	10.00 ± 0.00 (5)			9.80 ± .200 (5)			9.75 ± .250 (4)			10.20 ± .374 (5)		
P (MG %)		8.20 ± .408 (4)	8.10 ± .176 (5)			7.64 ± .144 (5)			7.63 ± .103 (4)			8.20 ± .341 (5)		
NA-(CL+CO_2)		16.00 ± 1.22 (4)	16.80 ± .663 (5)			14.20 ± .374 (5)			14.00 ± .577 (4)			17.20 ± .735 (5)		
CHOL (MG %)		47.25 ± .479 (4)	46.80 ± .860 (5)			47.00 ± 1.52 (5)			47.25 ± 2.39 (4)			55.80 ± 2.18 (5)	*	
TRIG (MG %)		95.50 ± 17.3 (4)	135.00 ± 22.2 (5)			109.40 ± 14.7 (5)			115.00 ± 20.4 (4)			111.60 ± 7.26 (5)		
BILI (MG %)		.10 ± 0.00 (4)	.12 ± .020 (5)		A	.16 ± .024 (5)		D	.15 ± .029 (4)		D	.10 ± 0.00 (5)		
SGOT (MU/ML)		98.75 ± 4.37 (4)	97.00 ± [illegible] (5)			111.80 ± 6.30 (5)			89.50 ± 6.36 (4)			88.40 ± 6.19 (5)		
SGPT (MU/ML)		41.25 ± 2.29 (4)	50.40 ± 3.23 (5)			46.40 ± 1.47 (5)			40.50 ± 2.06 (4)			36.60 ± 3.30 (5)		
LDH (MU/ML)		454.50 ± 172. (4)	627.80 ± 237. (5)		•	901.00 ± 248. (5)		•	535.75 ± 189. (4)		•	862.75 ± 404. (4)		•
ALK-P (MU/ML)		273.50 ± 39.3 (4)	368.75 ± 29.8 (4)			321.00 ± 30.8 (5)			326.75 ± 17.2 (4)			350.60 ± 54.7 (5)		
IRON (MCG %)		193.75 ± 19.2 (4)	206.00 ± 9.69 (5)			207.20 ± 15.7 (5)			226.00 ± 7.45 (4)			189.00 ± 11.0 (5)		
PROTFIN (GM %)		5.63 ± .193 (4)	6.24 ± .112 (5)	*		6.16 ± .117 (5)			6.00 ± .108 (4)			6.14 ± .087 (5)		
ALBUMIN (GM %)		4.93 ± .025 (4)	5.28 ± .074 (5)			5.20 ± .141 (5)			5.05 ± .087 (4)			5.28 ± .124 (5)		
GLOBULIN (GM%)		.70 ± .196 (4)	.96 ± .068 (5)			.96 ± .075 (5)			.95 ± .104 (4)			.86 ± .060 (5)		
A/G RATIO	+	10.65 ± 4.69 (4)	5.62 ± .413 (5)		•	5.60 ± .591 (5)		•	5.53 ± .641 (4)		•	6.32 ± .562 (5)		•

ENTRIES ARF MFANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARF ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 102

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF FEMALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
GLUCOSE (MG %)	*	155.33 ± 9.74 (3)	157.40 ± 4.12 (5)		158.00 ± 5.72 (5)		159.60 ± 7.83 (5)		136.00 ± .837 (5)	
BUN (MG %)		15.33 ± 1.33 (3)	18.60 ± 1.21 (5)		1[illegible].00 ± 1.45 (5)		18.40 ± .678 (5)		20.80 ± 1.98 (5)	
CREAT (MG %)		.50 ± .058 (3)	.36 ± .060 (5)	B	.50 ± .032 (5)	B	.64 ± .024 (5)	B	.58 ± .020 (5)	A
URIC ACID (MG)	*	2.27 ± .928 (3)	.82 ± .180 (5)	•	1.44 ± .172 (5)	•	1.64 ± .194 (5)	•	.98 ± .102 (5)	•
NA (MEQ/L)		147.00 ± .577 (3)	144.80 ± 1.02 (5)		141.60 ± 1.21 (5)	*	140.60 ± .400 (5)	+	142.80 ± .735 (5)	
K (MEQ/L)		5.23 ± .933 (3)	4.18 ± .285 (5)		4.98 ± .150 (5)		5.38 ± .351 (5)		5.34 ± .234 (5)	
CO_2 (MEQ/L)		23.33 ± 1.67 (3)	24.60 ± 1.33 (5)		26.60 ± .927 (5)		25.60 ± .927 (5)		25.80 ± .860 (5)	
CL (MEQ/L)		103.33 ± 1.20 (3)	104.00 ± 1.05 (5)		100.60 ± 1.17 (5)		101.00 ± .548 (5)		102.80 ± 1.02 (5)	
CA (MG %)		9.67 ± .333 (3)	10.00 ± 0.00 (5)		10.00 ± 0.00 (5)		10.20 ± .200 (5)		10.20 ± .200 (5)	
P (MG %)		8.03 ± .29[illegible] (3)	6.38 ± .397 (5)		6.42 ± .302 (5)		6.92 ± .379 (5)		7.08 ± .107 (5)	
$NA-(CL+CO_2)$		20.33 ± 1.45 (3)	16.20 ± 1.16 (5)		14.40 ± .245 (5)	+ A	14.00 ± .548 (5)	+ B	14.20 ± .663 (5)	+ A
CHOL (MG %)		60.33 ± 4.33 (3)	61.60 ± 1.91 (5)		65.00 ± 1.24 (5)		67.60 ± 5.30 (5)		88.00 ± 3.36 (5)	+ B
TRIG (MG %)		54.00 ± 11.4 (3)	64.80 ± 15.9 (5)		81.60 ± 17.2 (5)		63.20 ± 5.89 (5)		53.60 ± 8.77 (5)	
BILI (MG %)		.10 ± 0.00 (3)	.14 ± .024 (5)	C	.12 ± .020 (5)		.10 ± 0.00 (5)		.18 ± .020 (5)	D
SGOT (MU/ML)	*	133.00 ± 27.5 (3)	85.20 ± 8.74 (5)		82.60 ± 6.41 (5)		93.00 ± 1.92 (5)		82.60 ± 4.08 (5)	
SGPT (MU/ML)		36.33 ± 1.45 (3)	34.40 ± 3.60 (5)		36.40 ± 2.93 (5)		29.80 ± 2.13 (5)		22.40 ± 1.21 (5)	A
LDH (MU/ML)		308.33 ± 65.2 (3)	327.40 ± 104. (5)		482.00 ± 76.3 (5)		62[illegible].60 ± 128. (5)		428.00 ± 91.0 (5)	
ALK-P (MU/ML)		186.33 ± 34.1 (3)	237.40 ± 19.4 (5)		226.40 ± 27.7 (5)		250.20 ± 31.7 (5)		226.60 ± 19.0 (5)	
IRON (MCG %)		270.00 ± 16.8 (3)	299.40 ± 22.2 (5)		32[illegible].60 ± 48.5 (5)		302.60 ± 29.4 (5)		189.40 ± 16.0 (5)	
PROTEIN (GM %)		5.87 ± .167 (3)	6.24 ± .024 (5)		6.36 ± .147 (5)		6.[illegible]8 ± .124 (5)		6.58 ± .080 (5)	*
ALBUMIN (GM %)		5.27 ± .067 (3)	5.48 ± .086 (5)		5.26 ± .117 (5)		5.34 ± .098 (5)		5.40 ± .045 (5)	
GLOBULIN (GM%)		.60 ± .100 (3)	.76 ± .093 (5)		1.10 ± .100 (5)		1.04 ± .121 (5)		1.18 ± .037 (5)	* A
A/G RATIO	*	9.70 ± 1.20 (3)	7.76 ± 1.14 (5)		4.94 ± .495 (5)	*	5.44 ± .705 (5)		4.58 ± .111 (5)	B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 103

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF MALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
GLUCOSE (MG %)	*	148.00 ± 5.77 (5)	156.40 ± 13.4 (5)		142.60 ± 3.67 (5)		122.00 ± 5.57 (5)	*	124.20 ± 1.32 (5)	*
BUN (MG %)		16.60 ± 1.21 (5)	14.20 ± .583 (5)		18.00 ± 1.00 (5)		19.40 ± 1.36 (5)		16.60 ± 1.47 (5)	
CREAT (MG %)		.48 ± .020 (5)	.58 ± .020 (5)	B	.54 ± .024 (5)	A	.50 ± 0.00 (5)		.65 ± .040 (5)	+ C
URIC ACID (MG)	*	1.20 ± .128 (5)	1.48 ± .267 (5)		1.26 ± .133 (5)		1.28 ± .058 (5)		2.24 ± .341 (5)	*
NA (MEQ/L)		141.60 ± .678 (5)	143.80 ± .800 (5)	*	141.20 ± .374 (5)		142.80 ± .583 (5)		142.40 ± .400 (5)	
K (MEQ/L)		4.92 ± .171 (5)	5.12 ± .174 (5)		4.82 ± .132 (5)		5.10 ± .158 (5)		5.52 ± .128 (5)	
CO_2 (MEQ/L)		26.80 ± 1.24 (5)	27.20 ± .800 (5)		27.20 ± 1.02 (5)		27.40 ± 1.54 (5)		26.80 ± .800 (5)	
CL (MEQ/L)		100.80 ± .583 (5)	101.20 ± .200 (5)		100.00 ± .894 (5)		100.40 ± .927 (5)		99.20 ± 1.20 (5)	
CA (MG %)		10.20 ± .200 (5)	10.20 ± .200 (5)		9.80 ± .200 (5)		10.00 ± 0.00 (5)		10.00 ± 0.00 (5)	
P (MG %)	*	6.26 ± .194 (5)	6.18 ± .116 (5)		6.42 ± .275 (5)		6.16 ± .075 (5)		5.86 ± .051 (5)	
$NA-(CL+CO_2)$		14.00 ± .775 (5)	16.40 ± .245 (5)		14.00 ± .447 (5)		15.00 ± .316 (5)		16.40 ± .678 (5)	
CHOL (MG %)		41.80 ± 1.98 (5)	42.60 ± 2.38 (5)		40.40 ± 4.07 (5)		47.40 ± 1.60 (5)		68.40 ± 3.14 (5)	+ C
TRIG (MG %)	*	103.80 ± 24.3 (5)	101.00 ± 13.2 (5)		54.20 ± 6.06 (5)		40.60 ± 2.66 (5)	B	41.40 ± 7.43 (5)	B
BILI (MG %)		.16 ± .024 (5)	.10 ± 0.00 (5)	C	.12 ± .020 (5)	B	.16 ± .024 (5)		.20 ± 0.00 (5)	B
SGOT (MU/ML)	*	96.20 ± 12.4 (5)	117.20 ± 25.2 (5)		136.00 ± 12.1 (5)		104.60 ± 6.42 (5)		87.60 ± 5.78 (5)	
SGPT (MU/ML)		37.20 ± .860 (5)	29.60 ± 4.43 (5)		37.40 ± 4.25 (5)		25.80 ± 3.06 (5)		15.00 ± 2.07 (5)	+ C
LDH (MU/ML)		717.80 ± 267. (5)	595.00 ± 127. (5)		640.60 ± 91.0 (5)		765.00 ± 104. (5)		726.20 ± 151. (5)	
ALK-P (MU/ML)		217.40 ± 19.6 (5)	168.20 ± 26.6 (5)		154.60 ± 24.0 (5)		125.00 ± 13.8 (5)	B	97.00 ± 5.53 (5)	+ B
IRON (MCG %)		201.00 ± 12.5 (5)	171.20 ± 15.1 (5)		123.00 ± 3.70 (5)	+ B	132.80 ± 5.98 (5)	+ B	130.80 ± 7.91 (5)	+ B
PROTEIN (GM %)		6.20 ± .071 (5)	6.36 ± .129 (5)		5.90 ± .045 (5)		6.18 ± .136 (5)		6.18 ± .139 (5)	
ALBUMIN (GM %)		5.50 ± .100 (5)	5.66 ± .117 (5)		5.36 ± .121 (5)		5.78 ± .111 (5)		5.78 ± .102 (5)	
GLOBULIN (GM%)		.70 ± .078 (5)	.70 ± .032 (5)		.54 ± .136 (5)		.40 ± .095 (5)	A	.40 ± .045 (5)	A
A/G RATIO	+	8.22 ± .864 (5)	8.12 ± .325 (5)		7.82 ± .397 (4)		21.80 ± 8.90 (5)		15.12 ± 1.53 (5)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 104

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF FEMALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP		TREATMENT GROUPS .002 % IN DIET		T R	.01 % IN DIET		T R	.05 % IN DIET		T R	.25 % IN DIET		T R
GLUCOSE (MG %)	*	125.80 ± 3.41	(5)	108.60 ± 3.50	(5)	*	107.40 ± 6.00	(5)	*	150.20 ± 15.0	(5)		109.00 ± 3.63	(5)	*
BUN (MG %)		14.80 ± .860	(5)	17.40 ± 1.96	(5)		17.80 ± 1.07	(5)		21.20 ± 1.71	(5)		21.00 ± 1.79	(5)	
CREAT (MG %)		.56 ± .040	(5)	.60 ± 0.00	(5)		.58 ± .037	(5)		.68 ± .020	(5)	B	.56 ± .040	(5)	
URIC ACID (MG)	+	1.26 ± .129	(5)	1.59 ± .188	(5)		1.54 ± .068	(5)		2.20 ± .670	(5)		2.12 ± .128	(5)	+
NA (MEQ/L)	*	139.80 ± 1.53	(5)	138.40 ± .510	(5)		142.40 ± .245	(5)		141.00 ± .707	(5)		140.20 ± .374	(5)	
K (MEQ/L)	*	5.42 ± .287	(5)	5.02 ± .116	(5)		5.18 ± .159	(5)		5.44 ± .353	(5)		5.20 ± .084	(5)	
CO_2 (MEQ/L)		22.40 ± .510	(5)	22.20 ± .860	(5)		25.40 ± 1.03	(5)		20.20 ± 1.16	(5)		23.20 ± 1.07	(5)	
CL (MEQ/L)		101.20 ± 1.11	(5)	100.80 ± 1.02	(5)		101.80 ± .800	(5)		102.00 ± 1.14	(5)		101.40 ± .927	(5)	
CA (MG %)		10.00 ± 0.00	(5)	10.00 ± 0.00	(5)		10.20 ± .200	(5)		10.00 ± 0.00	(5)		10.20 ± .200	(5)	
P (MG %)		5.62 ± .246	(5)	5.80 ± .330	(5)		4.46 ± .242	(5)		5.30 ± .277	(5)		5.04 ± .231	(5)	
NA-(CL+CO_2)		16.20 ± .490	(5)	15.40 ± .600	(5)		15.20 ± .583	(5)		18.80 ± .583	(5)		15.60 ± .600	(5)	
CHOL (MG %)		67.40 ± 4.74	(5)	74.60 ± 7.80	(5)		74.20 ± 4.66	(5)		79.60 ± 4.63	(5)		109.80 ± 5.91	(5)	+ B
TRIG (MG %)		19.20 ± 2.46	(5)	28.40 ± 10.1	(5)		27.80 ± 4.42	(5)		25.20 ± 5.07	(5)		29.80 ± 5.81	(5)	
BILI (MG %)		.20 ± 0.00	(5)	.12 ± .020	(5)	C	.16 ± .024	(5)	B	.16 ± .024	(5)	B	.22 ± .020	(5)	
SGOT (MU/ML)	+	197.80 ± 63.4	(5)	131.20 ± 17.4	(5)	•	130.20 ± 14.4	(5)		149.80 ± 32.3	(5)		91.00 ± 6.32	(5)	•
SGPT (MU/ML)	+	57.20 ± 28.4	(5)	32.40 ± 4.42	(5)	•	25.20 ± 3.37	(5)	•	28.20 ± 2.56	(5)	•	13.20 ± 3.23	(5)	•
LDH (MU/ML)		921.00 ± 105.	(5)	1473.00 ± 201.	(5)		792.00 ± 80.1	(5)		542.00 ± 154.	(4)		509.20 ± 74.8	(5)	A
ALK-P (MU/ML)		84.60 ± 6.31	(5)	86.00 ± 9.85	(5)		93.00 ± 8.87	(5)		80.80 ± 2.94	(5)		75.40 ± 11.2	(5)	
IRON (MCG %)		367.20 ± 23.5	(5)	309.20 ± 36.2	(5)		279.80 ± 35.2	(5)		243.40 ± 42.8	(5)	A	223.00 ± 17.9	(5)	A
PROTEIN (GM %)		6.54 ± .075	(5)	6.38 ± .224	(5)		6.50 ± .164	(5)		6.26 ± .181	(5)		6.56 ± .154	(5)	
ALBUMIN (GM %)		5.84 ± .068	(5)	5.96 ± .297	(5)		6.12 ± .255	(5)		5.50 ± .400	(3)		6.28 ± .317	(5)	
GLOBULIN (GM%)		.70 ± .071	(5)	.42 ± .111	(5)		.46 ± .121	(5)		.57 ± .167	(3)		.50 ± .058	(4)	
A/G RATIO		8.72 ± .937	(5)	11.57 ± 1.79	(4)		10.27 ± .918	(4)		11.53 ± 3.17	(3)		12.35 ± 1.22	(4)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 10[illegible]

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF MALE RATS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
GLUCOSE (MG %)		135.60 ± 5.12 (5)	125.00 ± 7.64 (5)		153.00 ± 14.1 (5)		151.40 ± 12.8 (5)		148.60 ± 7.65 (5)	
BUN (MG %)		20.80 ± .800 (5)	17.00 ± 1.73 (5)		17.80 ± 1.53 (5)		14.80 ± 1.24 (5)	A	15.00 ± 1.05 (5)	A
CREAT (MG %)		.58 ± .020 (5)	.58 ± .020 (5)		.64 ± .060 (5)	A	.72 ± .037 (5)	B	.56 ± .024 (5)	
URIC ACID (MG)		1.40 ± .148 (5)	2.20 ± .453 (5)		1.82 ± .199 (5)		2.20 ± .217 (5)		1.90 ± .311 (5)	
NA (MEQ/L)		143.80 ± .970 (5)	144.80 ± .970 (5)		139.80 ± 1.39 (5)		141.00 ± .447 (5)		141.40 ± .812 (5)	
K (MEQ/L)	*	5.52 ± .097 (5)	5.82 ± .702 (5)		5.60 ± .308 (5)		5.76 ± .129 (5)		5.90 ± .432 (5)	
CO_2 (MEQ/L)		24.80 ± .490 (5)	22.20 ± 1.36 (5)		24.40 ± 1.08 (5)		26.40 ± 1.36 (5)		25.80 ± 1.20 (5)	
CL (MEQ/L)		104.20 ± .490 (5)	102.40 ± .872 (5)		101.60 ± .872 (5)		99.80 ± 1.16 (5)		102.00 ± 1.05 (5)	
CA (MG %)		10.00 ± 0.00 (5)	9.40 ± .245 (5)		9.60 ± .245 (5)		10.20 ± .374 (5)		10.60 ± .245 (5)	
P (MG %)	*	6.68 ± .116 (5)	7.54 ± .426 (5)		6.28 ± .372 (5)		7.26 ± .0[illegible] (5)	*	7.20 ± .265 (5)	
NA-(CL+CO_2)		14.80 ± .583 (5)	20.20 ± 1.36 (5)	* A	13.80 ± 1.32 (5)		14.80 ± .490 (5)		13.60 ± .400 (5)	
CHOL (MG %)		51.40 ± 3.03 (5)	52.20 ± 2.52 (5)		45.80 ± 3.73 (5)		46.60 ± 4.68 (5)		40.80 ± 2.73 (5)	
TRIG (MG %)	+	217.40 ± 52.5 (5)	51.00 ± 5.94 (5)	* D	77.00 ± 29.6 (5)	A	47.20 ± 14.3 (5)	* D	40.40 ± 6.17 (5)	* D
BILI (MG %)		.10 ± 0.00 (5)	.20 ± 0.00 (5)	+ D	.14 ± .024 (5)	C	.10 ± 0.00 (5)		.10 ± 0.30 (5)	
SGOT (MU/ML)		130.40 ± 12.5 (5)	133.80 ± 12.[illegible] (5)		118.00 ± 25.3 (5)		136.40 ± 23.6 (5)		102.20 ± 20.8 (5)	
SGPT (MU/ML)		54.60 ± 5.87 (5)	42.00 ± 5.14 (5)		36.40 ± 6.02 (5)		43.00 ± 7.16 (5)		36.80 ± 4.73 (5)	
LDH (MU/ML)		1538.00 ± 189. (5)	1285.00 ± 298. (5)		1064.00 ± 270. (5)		977.80 ± 239. (5)		556.80 ± 151. (5)	B
ALK-P (MU/ML)		288.40 ± 46.0 (5)	177.60 ± 15.7 (5)	A	179.40 ± 18.5 (5)	A	193.20 ± 21.1 (5)	A	165.20 ± 18.2 (5)	B
IRON (MCG %)		204.00 ± 11.2 (5)	193.60 ± 14.4 (5)		149.60 ± 8.95 (5)	A	160.80 ± 12.1 (5)		148.00 ± 12.5 (5)	A
PROTEIN (GM %)		6.12 ± .139 (5)	6.22 ± .120 (5)		6.00 ± .164 (5)		6.38 ± .156 (5)		6.30 ± .127 (5)	
ALBUMIN (GM %)		5.50 ± .063 (5)	5.72 ± .199 (5)		5.26 ± .211 (5)		5.38 ± .153 (5)		5.44 ± .093 (5)	
GLOBULIN (GM%)		.62 ± .107 (5)	.50 ± .084 (5)		.74 ± .060 (5)		1.00 ± .063 (5)	* B	.86 ± .040 (5)	
A/G RATIO	+	11.52 ± 3.68 (5)	14.26 ± 4.48 (5)	*	7.42 ± .896 (5)	*	5.46 ± .419 (5)		6.36 ± .206 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
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BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 106

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF FEMALE RATS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
GLUCOSE (MG %)		142.00 ± 6.77 (4)	111.20 ± 2.78 (5)	* A	123.00 ± 10.1 (3)		116.25 ± 4.87 (4)		115.00 ± 3.21 (3)	
BUN (MG %)		18.00 ± 1.47 (4)	16.20 ± .663 (5)		13.67 ± 1.20 (3)		15.00 ± 1.08 (4)		18.33 ± .333 (3)	
CREAT (MG %)		.57 ± .048 (4)	.58 ± .037 (5)		.50 ± 0.00 (3)	A	.70 ± .041 (4)	B	.63 ± .033 (3)	A
URIC ACID (MG)		1.77 ± .747 (4)	1.60 ± .164 (5)		1.80 ± .351 (3)		1.95 ± .222 (4)		1.27 ± .240 (3)	
NA (MEQ/L)		142.75 ± 1.65 (4)	141.40 ± .678 (5)		138.67 ± 3.38 (3)		139.50 ± .957 (4)		141.00 ± 1.53 (3)	
K (MEQ/L)		5.65 ± .636 (4)	5.14 ± .242 (5)		5.47 ± .393 (3)		5.38 ± .342 (4)		5.07 ± .267 (3)	
CO_2 (MEQ/L)		20.75 ± 2.69 (4)	23.40 ± 1.21 (5)		23.67 ± 1.45 (3)		22.75 ± .750 (4)		22.67 ± .333 (3)	
CL (MEQ/L)		105.00 ± .817 (4)	100.80 ± .860 (5)		100.00 ± 2.52 (3)		101.75 ± .750 (4)		101.00 ± 2.08 (3)	
CA (MG %)		10.00 ± .408 (4)	10.00 ± 0.00 (5)		10.00 ± 0.00 (3)		10.00 ± 0.00 (4)		9.67 ± .333 (3)	
P (MG %)		6.65 ± .409 (4)	6.24 ± .314 (5)		6.67 ± .088 (3)		5.65 ± .539 (4)		5.93 ± .233 (3)	
NA-(CL+CO_2)		17.00 ± 1.68 (4)	17.20 ± .800 (5)		15.00 ± 2.08 (3)		15.00 ± 1.29 (4)		17.33 ± 1.20 (3)	
CHOL (MG %)		68.50 ± 4.99 (4)	72.40 ± 4.93 (5)		78.67 ± 12.7 (3)		65.75 ± 3.25 (4)		77.33 ± 11.3 (3)	
TRIG (MG %)		64.25 ± 18.9 (4)	41.00 ± 14.0 (5)		27.67 ± 13.1 (3)		24.75 ± 7.15 (4)	A	36.50 ± .500 (2)	
BILI (MG %)		.13 ± .025 (4)	.18 ± .020 (5)	C	.10 ± 0.00 (3)	B	.10 ± 0.00 (4)	B	.10 ± 0.00 (3)	B
SGOT (MU/ML)		102.00 ± 13.3 (4)	97.40 ± 12.4 (5)		100.33 ± 23.1 (3)		89.50 ± 17.3 (4)		78.67 ± 10.8 (3)	
SGPT (MU/ML)		35.50 ± 6.14 (4)	20.20 ± 3.20 (5)	A	23.67 ± 3.33 (3)		27.75 ± 2.78 (4)		26.67 ± 3.18 (3)	
LDH (MU/ML)		501.50 ± 156. (4)	837.00 ± 117. (5)		864.67 ± 341. (3)		599.50 ± 55.4 (4)		266.67 ± 109. (3)	
ALK-P (MU/ML)	*	185.50 ± 46.5 (4)	110.60 ± 10.1 (5)		120.33 ± 30.4 (3)	•	87.75 ± 6.34 (4)	•	82.33 ± 7.88 (3)	•
IRON (MCG %)		342.25 ± 51.7 (4)	334.40 ± 23.8 (5)		346.33 ± 75.6 (3)		372.00 ± 19.6 (4)		249.33 ± 18.6 (3)	
PROTEIN (GM %)		6.25 ± .096 (4)	6.74 ± .136 (5)		6.50 ± .436 (3)		6.35 ± .064 (4)		6.00 ± .265 (3)	
ALBUMIN (GM %)		5.50 ± .108 (4)	5.84 ± .204 (5)		5.73 ± .410 (3)		5.50 ± .141 (4)		5.40 ± .100 (3)	
GLOBULIN (GM%)		.75 ± .064 (4)	1.10 ± .114 (5)		.77 ± .033 (3)		.85 ± .104 (4)		.60 ± .173 (3)	
A/G RATIO	*	7.55 ± .779 (4)	5.48 ± .428 (5)		7.47 ± .328 (3)		6.82 ± 1.03 (4)		10.90 ± 3.46 (3)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 107

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF MALE RATS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP		.002 % IN DIET		T R	.01 % IN DIET		T R	.05 % IN DIET		T R	.25 % IN DIET		T R
							TREATMENT GROUPS								
GLUCOSE (MG %)		125.20 ± 5.56	(5)	137.20 ± 2.54	(5)		119.40 ± 3.92	(5)		129.20 ± 4.62	(5)		119.80 ± 5.97	(5)	
BUN (MG %)		19.20 ± 1.32	(5)	16.40 ± 1.08	(5)		20.80 ± 1.36	(5)		15.60 ± 2.48	(5)		21.60 ± 1.72	(5)	
CREAT (MG %)		.72 ± .020	(5)	.72 ± .020	(5)		.64 ± .040	(5)	A	.54 ± .051	(5)	* B	.68 ± .020	(5)	
NA (MEQ/L)		143.20 ± .583	(5)	142.20 ± .374	(5)		144.80 ± .200	(5)		143.80 ± .583	(5)		144.20 ± .200	(5)	
K (MEQ/L)		5.18 ± .177	(5)	5.08 ± .162	(5)		5.10 ± .127	(5)		5.34 ± .221	(5)		5.48 ± .136	(5)	
CO_2(MEQ/L)		29.60 ± .927	(5)	28.60 ± .927	(5)		26.80 ± .374	(5)		27.20 ± .490	(5)		26.40 ± .748	(5)	
CL (MEQ/L)		101.60 ± 1.08	(5)	101.60 ± .678	(5)		101.80 ± .200	(5)		101.80 ± .860	(5)		102.00 ± .548	(5)	
CA (MG %)		10.00 ± 0.00	(5)	9.80 ± .200	(5)		10.20 ± .200	(5)		10.00 ± 0.00	(5)		10.00 ± 0.00	(5)	
P (MG %)		6.18 ± .285	(5)	6.30 ± .192	(5)		5.94 ± .183	(5)		6.64 ± .260	(5)		6.22 ± .235	(5)	
NA-(CL+CO_2)		12.00 ± .837	(5)	12.60 ± .316	(5)		16.20 ± .374	(5)	+ A	14.80 ± .583	(5)	*	15.80 ± .374	(5)	
CHOL (MG %)		47.60 ± 3.66	(5)	38.40 ± 2.34	(5)		47.80 ± 3.71	(5)		46.40 ± 2.29	(5)		55.00 ± 3.11	(5)	
TRIG (MG %)	*	81.00 ± 27.1	(5)	71.00 ± 7.80	(5)		51.00 ± 5.52	(5)	*	x			x		
BILI (MG %)		.18 ± .020	(5)	.16 ± .024	(5)	A	.14 ± .024	(5)	B	.12 ± .020	(5)	B	.10 ± 0.00	(5)	C
SGOT (MU/ML)		128.80 ± 14.7	(5)	118.80 ± 13.6	(5)		107.60 ± 9.76	(5)		112.40 ± 13.9	(5)		132.60 ± 20.8	(5)	
SGPT (MU/ML)		40.20 ± 5.18	(5)	34.20 ± 4.02	(5)		31.60 ± 3.66	(5)		37.00 ± 2.39	(5)		40.40 ± 7.03	(5)	
LDH (MU/ML)		1305.00 ± 215.	(5)	1141.00 ± 225.	(5)		1130.20 ± 174.	(5)		647.50 ± 237.	(4)	A	965.00 ± 139.	(5)	
ALK-P (MU/ML)		162.40 ± 20.2	(5)	137.00 ± 14.2	(5)		183.80 ± 32.5	(5)		119.80 ± 8.85	(5)		157.60 ± 16.0	(5)	
IRON (MCG %)		181.60 ± 12.9	(5)	148.20 ± 7.85	(5)		185.00 ± 12.0	(5)		147.60 ± 5.82	(5)		150.00 ± 13.7	(5)	
PROTEIN (GM %)		6.12 ± .097	(5)	6.08 ± .058	(5)		6.46 ± .150	(5)		6.28 ± .111	(5)		6.28 ± .153	(5)	
ALBUMIN (GM %)	*	5.60 ± .105	(5)	5.50 ± .032	(5)		3.06 ± .051	(5)	+ C	2.98 ± .037	(5)	+ C	2.80 ± .123	(5)	+ C
GLOBULIN (GM%)		.52 ± .037	(5)	.58 ± .074	(5)		3.40 ± .105	(5)	+ D	3.30 ± .084	(5)	+ D	3.48 ± .107	(5)	+ D
A/G RATIO	+	10.88 ± .997	(5)	10.14 ± 1.2.	(5)		.90 ± 0.00	(5)	+ D	.92 ± .020	(5)	+ D	.82 ± .058	(5)	+ D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .
x TRIGLYCERIDE DATA MISSING.
NOTE: URIC ACID WAS NOT DETERMINED.

TABLE 105

EFFECTS OF TNT ON CLINICAL CHEMISTRY
OF FEMALE RATS AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .002 % IN DIET	T R	.01 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R
GLUCOSE (MG %)		124.60 ± 2.01 (5)	124.20 ± 4.77 (5)		126.60 ± 5.62 (5)		132.00 ± 4.14 (4)		123.00 ± 7.02 (3)	
BUN (MG %)	*	16.80 ± 2.48 (5)	15.20 ± .800 (5)		17.20 ± .860 (5)		17.50 ± .645 (4)		17.67 ± .882 (3)	
CREAT (MG %)		.70 ± 0.00 (5)	.82 ± .020 (5)		.72 ± .037 (5)		.48 ± .146 (5)		.36 ± .189 (5)	A
NA (MEQ/L)		142.60 ± .400 (5)	143.00 ± .447 (5)		143.20 ± .374 (5)		144.00 ± .913 (4)		143.00 ± 1.15 (3)	
K (MEQ/L)		5.14 ± .186 (5)	5.22 ± .177 (5)		5.02 ± .193 (5)		5.18 ± .206 (4)		5.17 ± .203 (3)	
CO_2(MEQ/L)		27.40 ± .510 (5)	24.20 ± .860 (5)		22.60 ± .812 (5)	*	22.75 ± 1.44 (4)	*	21.00 ± .577 (3)	
CL (MEQ/L)		104.60 ± .510 (5)	106.80 ± .583 (5)		106.80 ± 1.02 (5)		105.00 ± .408 (4)		108.00 ± 1.15 (3)	
CA (MG %)		10.20 ± .200 (5)	10.60 ± .245 (5)		10.00 ± 0.00 (5)		10.25 ± .250 (4)		10.00 ± 0.00 (3)	
P (MG %)		4.60 ± .407 (5)	4.04 ± .295 (5)		4.26 ± .117 (5)		5.65 ± .125 (4)		4.73 ± .133 (3)	
NA-(CL+CO_2)		10.40 ± .245 (5)	12.00 ± .548 (5)		13.80 ± .490 (5)	+ A	16.25 ± .479 (4)	+ C	14.00 ± .577 (3)	
CHOL (MG %)	*	71.40 ± 6.35 (5)	65.20 ± 4.80 (5)		66.60 ± 5.27 (5)		71.75 ± 4.71 (4)		43.60 ± 17.8 (5)	
TRIG (MG %)		29.60 ± 2.96 (5)	25.40 ± 2.59 (5)		32.33 ± 6.44 (3)	+	x		x	
BILI (MG %)		.20 ± 0.00 (5)	.16 ± .024 (5)	B	.14 ± .024 (5)	B	.08 ± .049 (5)	D	.10 ± 0.00 (3)	D
SGOT (MU/ML)	*	108.40 ± 3.87 (5)	103.40 ± 9.61 (5)		124.20 ± 9.12 (5)		96.50 ± 11.5 (2)		127.67 ± 40.9 (3)	
SGPT (MU/ML)		32.60 ± 2.94 (5)	28.20 ± 2.71 (5)		33.40 ± 2.25 (5)		31.50 ± 6.50 (2)		44.00 ± 10.0 (3)	
LDH (MU/ML)		599.40 ± 90.4 (5)	505.60 ± 106. (5)		463.20 ± 58.6 (5)		688.50 ± 211. (2)		729.33 ± 171. (3)	
ALK-P (MU/ML)	*	89.20 ± 13.6 (5)	99.00 ± 10.6 (5)		117.20 ± 9.67 (5)		115.25 ± 51.5 (4)		88.33 ± 7.69 (3)	
IRON (MCG %)		345.40 ± 36.6 (5)	392.00 ± 14.9 (5)		[illegible]14.40 ± 13.9 (5)		276.00 ± 20.0 (4)		355.57 ± 30.9 (3)	
PROTEIN (GM %)		6.28 ± .124 (5)	6.58 ± .132 (5)		6.34 ± .087 (5)		6.60 ± .280 (4)		6.63 ± .033 (3)	
ALBUMIN (GM %)	*	6.18 ± .180 (5)	6.76 ± .240 (5)		3.14 ± .024 (5)	+ C	3.15 ± .150 (4)	+ C	3.20 ± .058 (3)	+ C
GLOBULIN (GM%)		.25 ± .050 (2)	.30 ± 0.00 (1)	*	3.22 ± .078 (5)	+ *	3.45 ± .132 (4)	+ *	3.43 ± .067 (3)	+ *
A/G RATIO	+	23.50 ± 4.60 (2)	20.00 ± 0.00 (1)	*	.98 ± .037 (5)	*	.90 ± 0.00 (4)	*	.93 ± .033 (3)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .
X- TRIGLYCERIDE DATA MISSING.
NOTE: URIC ACID WAS NOT DETERMINED.

Table 109

MICROSCOPIC LESIONS IN MALE RATS AFTER 4 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.002	0.01	0.05	0.25
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Colon					
Parasitism					181,182
Kidney					
Casts, hyaline				162	
Lymphocytes - interstitial	105				
Lung					
Alveolar collapse	101,102			161,162,163	181,184,185
Alveolar dilation	102			162,163,165	181,184,185
Hemorrhage				165	182
Respiratory disease - chronic	101,102,103 104,105			161,162,163 164,165	181,183,185
Lymph node					
Regeneration	103			163,164	
Spleen					
Pigmentation (hemosiderosis)					181,182,183 184,185
Testes					
Atrophy				162	181,182,183 184,185
Hyperplasia of interstitial cells					181,182,183 184,185
Thymus					
Hemorrhage	102				
Thyroid					
Cysts				163	
Trachea					
Inflammation - chronic	105			162	

Table 110

MICROSCOPIC LESIONS IN FEMALE RATS AFTER 4 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.002	0.01	0.05	0.25
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Cecum					
Parasitism					285
Colon					
Parasitism					285
Lung					
Alveolar collapse				262,265	281,282,283 284
Alveolar dilation				262,265	281,282,283 284
Hemorrhage				261,263	
Respiratory disease - chronic	201,202,203 204,205			261,262,263 264,265	281,282,283 284,285
Spleen					
Pigmentation (hemosiderosis)				262	281,282,283 284,285
Thymus					
Congestion	205				
Hemorrhage	201,204				
Trachea					
Inflammation - chronic				264	

Table 111

MICROSCOPIC LESIONS IN MALE RATS AFTER 13 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.002	0.01	0.05	0.25
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Adrenals					
Cells - vacuolated	115			173,174,175	
Epididymis					
Atrophy					191,192,193 194,195
Kidney					
Lymphocytes - interstitial					192
Nephrosis				171,172,173	
Lung					
Alveolar collapse	113,114,115			171,172,173 174,175	192,194,195
Alveolar dilation	113			171,172,175	192
Congestion	113,114				
Respiratory disease - chronic	113,114			171,172,174 175	192,194,195
Spleen					
Pigmentation (hemosiderosis)				171	191,192,193 194,195
Testes					
Atrophy					191,192,193 194,195
Hyperplasia of interstitial dells					191,192,193 194,195
Trachea					
Inflammation - chronic				172	

MICROSCOPIC LESIONS IN FEMALE RATS AFTER 13 WEEKS OF [illegible] TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.002	0.01	0.05	0.25
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Kidney					
Lymphocytes - interstitial					291
Liver					
Lymphocytes - parenchymal				275	291
Lymphocytes - paravascular					295
Lung					
Alveolar collapse	211,212,214			271,272,273	291,292,293
	215			274,275	294,295
Alveolar dilation	215,211,212			271,273,275	291,292,293
					294,295
Alveolar histiocytosis	213				
Hemorrhage	213,214			273	292
Respiratory disease - chronic	213,214,215			271,272,273	291,292,293
				274,275	294,295
Spleen					
Pigmentation (hemosiderosis)	213,215			271,273,275	291,292,293
					294,295
Uterus					
Ectasia (dilated)	212			271,275	293,294

Table 113

MICROSCOPIC LESIONS IN MALE RATS AFTER 4 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (% in Feed)				
	0	0.002	0.01	0.05	0.25
	Group Designation				
	A0	A1	A2	3	A4
	Animal Number				
Adrenals					
Lymphocytes - parenchymal			146		
Vacuolated cells			146		
Heart					
Lymphocytes - parenchymal				166	
Kidney					
Lymphocytes - parenchymal				168/169	
Lymphocytes - paravascular			146		
Regeneration	109		149	167,168,169	190
Lung					
Alveolar collapse	106,107,108	126	146,147,149	169	186,188,189
	109,110		150		190
Alveolar dilation			146/150	169	186,188,189
					190
Alveolar histiocytosis	108				
Hemorrhage		127,128,129	146,147,148	166,168,169	188,189
		130	149,150		
Respiratory disease - chronic	106,107,108	126,127,128	146,147,148	166,167,168	186,187,188
	109,110	129,130	149,150	169,170	189,190
Lymph node					
Hyperplasia			149		190
Pancreas					
Lymphocytes - paravascular					190
Spleen					
Pigmentation (hemosiderosis)					190
Testes					
Atrophy	107				186,187,188
					189,190

Table 113

MICROSCOPIC LESIONS IN MALE RATS AFTER 4 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

(Concluded)

Organ/Lesion	Dose Level (% in Feed)				
	0	0.002	0.01	0.05	0.25
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Testes					
Hyperplasia of interstitial cells					186,187,188
					189,190
Thymus					
Hyperplasia		130			
Trachea					
Inflammation - chronic			149		186

Table 114

MICROSCOPIC LESIONS IN FEMALE RATS AFTER 4 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (% in Feed)				
	0	0.002	0.01	0.05	0.25
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Kidney					
Hydronephrosis					287
Lymphocytes - parenchymal				267	
Lymphocytes - paravascular		229			
Regeneration	208			267	
Lung					
Alveolar collapse	207,208,209	226,227,228	246,248,249	267,268,269	288,289,290
		229	250	270	
Alveolar dilation			246,248,249	269/270	289,290
Hemorrhage	210	228	247	266,267,269	286,287,288
				270	290
Respiratory disease - chronic	206,207,208	226,227,228	246,247,248	266,267,268	286,287,288
	209,210	229,230	249,250	269,270	289,290
Spleen					
Pigmentation (hemosiderosis)					286,287,288
					289
Uterus					
Ectasia - dilated		226,228,229	246,250	269,270	290

MICROSCOPIC LESIONS IN MALE RATS AFTER [illegible] WEEKS OF [illegible] TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (% in Feed)				
	0	0.002	0.01	0.05	0.25
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Colon					
Parasitism	119				
Epididymus					
Atrophy					196,197,198
					199,200
Heart					
Necrosis				178	
Kidney					
Lymphocytes - paravascular	118			176	199
Lung					
Alveolar collapse	116,117,118			177,178	199,200,198
	119				
Alveolar dilation	117,118,119			178	199,200
Hemorrhage	118,119				
Respiratory disease - chronic	116,117,118			177,178,179	196,197,199
	119,120			180	200
Lymph nodes					
Edema					198
Prostate					
Hyperplasia					200
Spleen					
Pigmentation (hemosiderosis)	116,117			176,177,178	196,197,198
					199,200
Testes					
Atrophy	116			180	196,197,198
					199,200
Trachea					
Inflammation				176,178,179	196,198
				180	

Table 116

MICROSCOPIC LESIONS IN FEMALE RATS AFTER 13 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (% in Feed)				
	0	0.002	0.01	0.05	0.25
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Adrenal					
Congestion	218				
Eye					
Papilloma in vitreous				280	
Kidney					
Hydronephrosis	217				
Lymphocytes - interstitial				276,279	
Lymphocytes - parenchymal					296,298
Lymphocytes - paravascular	216				
Lung					
Alveolar collapse	216,218,220			277,278,279	296,299
Alveolar dilation	216,218,220			277/279	296,299
Hemorrhage				278,279,280	298,300
Respiratory disease - chronic	216,218,219 220			276,277,278 279,280	296,297,298 299,300
Lymph node					
Hemorrhage				279	
Pituitary					
Cysts					298
Spleen					
Pigmentation (hemosiderosis)	216,220			276,277,279 280	
Trachea					
Inflammation - chronic				279	
Uterus					
Ectasia - dilated	216,220				296,299

TABLE 117

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF MALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
INITIAL		22.3 ± .572 (20)	21.1 ± .743 (20)		21.9 ± .584 (20)		21.9 ± .822 (20)		21.7 ± .636 (20)	
WEEK 1		23.8 ± .749 (20)	22.7 ± .798 (20)		22.7 ± .590 (20)		21.6 ± 1.11 (20)		19.9 ± .808 (20)	*
WEEK 2		23.3 ± .808 (20)	22.7 ± .909 (20)		22.8 ± .706 (19)		23.6 ± 1.15 (19)		20.3 ± .895 (19)	
WEEK 3		24.9 ± .747 (20)	26.0 ± .896 (20)		25.3 ± .802 (19)		25.7 ± 1.14 (19)		24.9 ± .910 (19)	
WEEK 4		27.0 ± .806 (20)	26.2 ± .832 (20)		25.8 ± .870 (19)		27.2 ± 1.32 (19)		26.6 ± .899 (19)	
WEEK 5		29.8 ± 1.04 (15)	30.7 ± 1.37 (10)		29.7 ± 1.60 (10)		24.7 ± 1.13 (10)		28.7 ± 1.44 (9)	
WEEK 6		31.5 ± .844 (15)	31.1 ± 1.16 (10)		30.6 ± 1.98 (10)		27.6 ± 1.21 (9)		30.0 ± 1.13 (9)	
WEEK 7		31.1 ± .827 (15)	32.7 ± 1.32 (10)		31.2 ± 1.85 (10)		29.0 ± 1.21 (9)		32.0 ± 1.13 (9)	
WEEK 8		34.1 ± 1.41 (15)	34.1 ± 1.17 (10)		31.9 ± 1.91 (10)		31.0 ± 1.34 (9)		33.4 ± 1.19 (9)	
WEEK 9		31.9 ± .809 (10)	33.3 ± 1.13 (10)		31.5 ± 1.96 (10)		30.9 ± 1.23 (9)		32.9 ± 1.09 (9)	
WEEK 10		32.6 ± 1.00 (10)	36.4 ± 1.17 (10)		33.4 ± 2.42 (10)		31.5 ± 1.38 (9)		32.9 ± 1.34 (9)	
WEEK 11		34.8 ± .854 (10)	38.0 ± 1.10 (10)		35.0 ± 2.21 (10)		33.7 ± 1.48 (9)		35.6 ± 1.21 (9)	
WEEK 12	*	33.8 ± .680 (10)	35.9 ± 1.25 (10)		33.3 ± 2.04 (10)		32.8 ± 1.33 (9)		33.8 ± 1.30 (9)	
WEEK 13		34.2 ± .929 (10)	35.7 ± 1.31 (10)		35.9 ± 1.30 (9)		33.3 ± 1.82 (9)		33.1 ± 1.11 (9)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 118

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF FEMALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
INITIAL		23.1 ± .335 (20)	22.4 ± .520 (20)		23.0 ± .420 (20)		23.0 ± .484 (20)		23.2 ± .354 (20)	
WEEK 1		22.5 ± .438 (20)	22.8 ± .536 (20)		24.0 ± .649 (20)		20.7 ± .561 (20)		18.9 ± .431 (20)	+ A
WEEK 2		21.5 ± .520 (20)	22.1 ± .652 (20)		23.5 ± .759 (20)		21.4 ± .432 (20)		19.3 ± .594 (20)	
WEEK 3		23.1 ± .715 (20)	25.0 ± .596 (20)		25.9 ± .624 (20)	*	24.6 ± .372 (20)		22.1 ± .689 (20)	
WEEK 4		24.5 ± .790 (20)	25.5 ± .639 (20)		26.3 ± .633 (20)		25.9 ± .406 (20)		24.0 ± .686 (20)	
WEEK 5		25.1 ± .899 (15)	28.5 ± .969 (10)		29.7 ± .967 (10)	*	27.6 ± .618 (10)		24.5 ± .719 (10)	
WEEK 6	+	25.9 ± 1.31 (15)	29.2 ± 1.01 (10)		30.0 ± .931 (10)	*	28.4 ± .400 (10)		26.4 ± .521 (10)	
WEEK 7		26.7 ± 1.12 (15)	29.8 ± .964 (10)		29.6 ± .833 (10)		29.3 ± .775 (10)		27.2 ± .593 (10)	
WEEK 8		26.7 ± 1.16 (14)	31.7 ± .955 (10)	*	32.5 ± .885 (10)	+ A	30.8 ± .786 (10)		28.3 ± .559 (10)	
WEEK 9		25.9 ± 1.30 (9)	31.1 ± .983 (10)	*	30.6 ± 1.06 (10)	*	28.2 ± .757 (10)		27.2 ± .854 (10)	
WEEK 10		25.0 ± 1.26 (9)	29.6 ± 1.33 (10)		32.3 ± .955 (10)	+ A	29.2 ± .680 (10)		28.6 ± .733 (10)	
WEEK 11		27.8 ± 1.36 (9)	33.9 ± .924 (10)	+ A	33.4 ± 1.02 (10)	+	32.2 ± .772 (10)		30.7 ± .616 (10)	
WEEK 12		26.8 ± 1.36 (9)	32.5 ± .922 (10)	+	32.5 ± .946 (10)	+	31.6 ± .670 (10)	*	30.2 ± .786 (10)	
WEEK 13	*	26.1 ± 1.55 (9)	31.9 ± 1.11 (10)	*	32.1 ± 1.08 (10)	*	30.6 ± .521 (10)	*	29.6 ± .600 (10)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 119

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF MALE MICE AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
WEEK 1		1.50 ± .793 (20)	1.65 ± .730 (20)		.80 ± .631 (20)		-.25 ± .791 (20)	B	-1.85 ± .608 (20)	* D
WEEK 2		-.50 ± .420 (20)	0.00 ± .543 (20)	•	0.00 ± .419 (19)	•	1.63 ± .392 (19)	*	.16 ± .392 (19)	•
WEEK 3		1.60 ± .419 (20)	3.20 ± .296 (20)		2.47 ± .377 (19)		2.16 ± .473 (19)		4.63 ± .298 (19)	+ C
WEEK 4	*	2.15 ± .274 (20)	.25 ± .333 (20)	+ D	.47 ± .594 (19)	* A	1.47 ± .362 (19)		1.68 ± .390 (19)	
WEEK 5		2.27 ± .521 (15)	4.20 ± .772 (10)		2.50 ± .563 (10)		1.30 ± .559 (10)		2.22 ± .434 (9)	
WEEK 6		1.67 ± .599 (15)	.40 ± .733 (10)		.90 ± .433 (10)		2.22 ± .741 (9)		1.33 ± .500 (9)	
WEEK 7		-.33 ± .319 (15)	1.60 ± .371 (10)	*	60 ± .452 (10)	[illegible]	1.44 ± .444 (9)		2.00 ± .500 (9)	+
WEEK 8	+	3.00 ± 1.32 (15)	1.40 ± .371 (10)		.70 ± .260 (10)	C	2.00 ± .236 (9)		1.44 ± .294 (9)	
WEEK 9		-.70 ± .367 (10)	-.80 ± .389 (10)	•	-.40 ± .452 (10)	•	-.11 ± .261 (9)	•	-.56 ± .556 (9)	•
WEEK 10	*	.70 ± .4[illegible] (10)	3.10 ± .233 (10)	+ •	1.90 ± .752 (10)	•	.89 ± .309 (9)	•	0.00 ± .553 (9)	•
WEEK 11		2.20 ± .573 (10)	1.60 ± .306 (10)		1.60 ± .718 (10)		1.89 ± .351 (9)		2.67 ± .527 (9)	
WEEK 12		-1.00 ± .365 (10)	-2.10 ± .623 (10)	•	-1.70 ± .335 (10)	•	-.89 ± .423 (9)	•	-1.78 ± .813 (9)	•
WEEK 13	*	.40 ± .718 (10)	-.20 ± .359 (10)	•	.89 ± .564 (9)	•	.56 ± 1.06 (9)	•	-.67 ± 1.31 (9)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 120

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF FEMALE MICE AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
WEEK 1		-.65 + .393 (20)	.45 + .587 (20)	•	1.05 + .438 (20)		-2.30 + .665 (20)		-4.40 + .444 (20)	+
WEEK 2		-1.05 + .461 (20)	-.70 + .448 (20)	•	-.55 + .526 (20)	•	.65 + .437 (20)	•	.45 + .613 (20)	•
WEEK 3		1.70 + .385 (20)	2.85 + .284 (20)		2.45 + .312 (20)		3.25 + .215 (20)		2.85 + .437 (20)	
WEEK 4		1.30 + .263 (20)	.60 + .222 (20)	A	.40 + .234 (20)	B	1.20 + .247 (20)		1.80 + .321 (20)	
WEEK 5	*	1.27 + .431 (15)	2.90 + .233 (10)	*	3.60 + .221 (10)	+	2.50 + .453 (10)		2.40 + .221 (10)	*
WEEK 6		.73 + .628 (15)	.70 + .335 (10)	•	.30 + .597 (10)	•	.80 + .467 (10)	•	1.90 + .433 (10)	•
WEEK 7	+	.87 + .827 (15)	.60 + .371 (10)	•	-.40 + .581 (10)	•	.90 + .504 (10)	•	.80 + .133 (10)	•
WEEK 8	*	.07 + .267 (14)	1.90 + .277 (10)	+ •	2.90 + .315 (10)	+ •	1.50 + .342 (10)	* •	1.10 + .100 (10)	* •
WEEK 9		1.33 + .441 (9)	-.60 + .340 (10)	* D	-1.90 + .277 (10)	+ D	-2.60 + .306 (10)	+ D	-1.10 + .379 (10)	+ D
WEEK 10	+	-.89 + .588 (9)	-1.50 + 1.02 (10)	•	1.70 + .495 (10)	*	1.00 + .211 (10)	*	1.40 + .427 (10)	*
WEEK 11	+	2.78 + .547 (9)	4.30 + 1.33 (10)		1.10 + .277 (10)	* B	3.00 + .333 (10)		2.10 + .277 (10)	
WEEK 12		-1.00 + .333 (9)	-1.40 + .340 (10)	•	-.90 + .277 (10)	•	-.60 + .400 (10)	•	-.50 + .307 (10)	•
WEEK 13		-.67 + .500 (9)	-.60 + .499 (10)	•	-.40 + .618 (10)	•	-1.00 + .577 (10)		-.60 + .521 (10)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 121

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF MALE MICE DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
INITIAL		22.3 ± .572 (20)	20.4 ± 1.50 (5)		22.4 ± .678 (5)		23.6 ± 1.36 (5)		22.2 ± .970 (5)	
WEEK 1		23.8 ± .749 (20)	22.6 ± 1.17 (5)		21.4 ± 1.08 (5)		22.4 ± 2.73 (5)		20.6 ± 1.81 (5)	
WEEK 2		23.3 ± .808 (20)	24.2 ± 1.77 (5)		19.7 ± 1.25 (4)		27.2 ± 1.70 (4)		19.2 ± 2.06 (5)	
WEEK 3		24.9 ± .747 (20)	26.6 ± 1.94 (5)		22.7 ± 2.29 (4)		30.2 ± 1.44 (4)		23.4 ± 1.40 (5)	
WEEK 4		27.0 ± .806 (20)	27.6 ± 2.20 (5)		24.7 ± 2.17 (4)		32.7 ± 1.60 (4)		27.0 ± 1.10 (5)	
WEEK 5		29.8 ± 1.04 (15)	26.4 ± .872 (5)		27.2 ± 1.65 (4)		34.7 ± 1.31 (4)		29.8 ± 1.28 (5)	
WEEK 6		31.5 ± .844 (15)	29.8 ± 1.74 (5)		27.7 ± 1.93 (4)		34.5 ± 1.94 (4)		32.6 ± 1.44 (5)	
WEEK 7		31.1 ± .827 (15)	31.4 ± 2.29 (5)		28.2 ± 1.75 (4)		35.7 ± 1.89 (4)		35.2 ± 1.39 (5)	
WEEK 8		34.1 ± 1.41 (15)	30.2 ± 2.60 (5)		30.2 ± 2.29 (4)		38.0 ± 1.83 (4)		35.6 ± 1.33 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 122

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF FEMALE MICE DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
INITIAL		23.1 ± .335 (20)	21.6 ± 1.50 (5)		22.4 ± .400 (5)		22.8 ± .800 (5)		23.2 ± .490 (5)	
WEEK 1		22.5 ± .438 (20)	23.8 ± 1.43 (5)		24.0 ± .707 (5)		21.4 ± .600 (5)		18.2 ± .970 (5)	+ A
WEEK 2	*	21.5 ± .520 (20)	24.4 ± 1.72 (5)		23.0 ± 1.79 (5)		23.6 ± .245 (5)	+	20.4 ± 1.03 (5)	
WEEK 3		23.1 ± .715 (20)	26.4 ± 1.50 (5)		25.6 ± 1.57 (5)		25.8 ± .583 (5)		23.6 ± 1.36 (5)	
WEEK 4		24.5 ± .790 (20)	27.0 ± 1.58 (5)		26.0 ± 1.52 (5)		27.6 ± .678 (5)		25.6 ± 1.29 (5)	
WEEK 5		25.1 ± .899 (15)	28.0 ± 1.52 (5)		20.6 ± 1.12 (5)		28.0 ± 1.53 (5)		26.0 ± 1.56 (5)	
WEEK 6		25.9 ± 1.31 (15)	28.8 ± 1.36 (5)		27.4 ± 1.17 (5)		28.0 ± .707 (5)		27.4 ± 1.94 (5)	
WEEK 7		26.7 ± 1.12 (15)	30.0 ± 1.58 (5)		28.8 ± 1.66 (5)		28.8 ± .970 (5)		29.6 ± 1.96 (5)	
WEEK 8		26.7 ± 1.16 (14)	28.8 ± 1.46 (5)		31.4 ± 1.63 (5)		31.0 ± .894 (5)		30.8 ± 2.08 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 123

EFFECTS OF TNT ON BODY WEIGHTS (G)
OF MALE MICE DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
INITIAL		22.3 ± .572 (20)	21.2 ± .970 (5)		22.8 ± 1.24 (5)		19.8 ± 1.11 (5)		21.4 ± 1.44 (5)	
WEEK 1		23.8 ± .749 (20)	23.8 ± 1.02 (5)		23.8 ± .583 (5)		19.6 ± 1.03 (5)		18.2 ± 1.07 (5)	* A
WEEK 2		23.3 ± .808 (20)	23.2 ± 1.66 (5)		24.6 ± 1.17 (5)		21.0 ± 1.00 (5)		18.6 ± 1.12 (5)	
WEEK 3		24.9 ± .747 (20)	26.6 ± 1.54 (5)		26.2 ± 1.24 (5)		22.6 ± 1.72 (5)		23.0 ± 1.05 (5)	
WEEK 4		27.0 ± .806 (20)	26.2 ± 1.32 (5)		24.2 ± 1.66 (5)		23.2 ± 2.03 (5)		24.2 ± 1.16 (5)	
WEEK 5		29.8 ± 1.04 (15)	29.8 ± 2.35 (5)		26.6 ± 2.50 (5)		24.2 ± 1.85 (5)		26.2 ± 1.39 (5)	
WEEK 6		31.5 ± .844 (15)	32.2 ± 1.93 (5)		26.6 ± 3.08 (5)		28.5 ± 1.26 (4)		28.4 ± 1.36 (5)	
WEEK 7		31.1 ± .827 (15)	33.0 ± 2.21 (5)		28.0 ± 3.11 (5)		30.5 ± .957 (4)		31.4 ± 1.69 (5)	
WEEK 8		34.1 ± 1.41 (15)	34.0 ± 2.07 (5)		29.0 ± 3.45 (5)		32.5 ± .957 (4)		33.2 ± 1.71 (5)	
WEEK 9		31.9 ± .809 (10)	32.8 ± 1.85 (5)		27.6 ± 3.08 (5)		32.0 ± 1.08 (4)		32.2 ± 1.28 (5)	
WEEK 10		32.6 ± 1.00 (10)	36.0 ± 1.82 (5)		27.8 ± 3.09 (5)		32.7 ± 1.11 (4)		31.2 ± 1.71 (5)	
WEEK 11		34.8 ± .854 (10)	37.6 ± 1.44 (5)		30.6 ± 3.47 (5)		34.2 ± 1.31 (4)		35.0 ± 1.52 (5)	
WEEK 12	*	33.8 ± .680 (10)	37.0 ± 1.70 (5)		29.4 ± 3.27 (5)		33.2 ± 1.03 (4)		31.4 ± 1.12 (5)	
WEEK 13		34.2 ± .929 (10)	37.4 ± 1.72 (5)		33.5 ± 2.47 (4)		36.5 ± .866 (4)		34.0 ± 1.22 (5)	
WEEK 14		36.4 ± .927 (5)	37.2 ± 1.59 (5)		32.7 ± 1.84 (4)		35.0 ± .913 (4)		35.8 ± 1.36 (5)	
WEEK 15		38.4 ± 1.21 (5)	39.6 ± 2.06 (5)		34.5 ± 1.66 (4)		35.7 ± 1.11 (4)		40.0 ± 1.34 (5)	
WEEK 16		38.2 ± 1.36 (5)	38.8 ± 1.77 (5)		36.7 ± 1.18 (4)		36.0 ± .707 (4)		39.0 ± .707 (5)	
WEEK 17		36.6 ± .980 (5)	37.4 ± 1.44 (5)		34.2 ± 1.38 (4)		35.2 ± .750 (4)		38.4 ± .980 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 124

EFFECTS OF TNT ON BODY WEIGHTS (C)
OF FEMALE MICE DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
INITIAL		23.1 ± .335 (20)	22.6 ± .400 (5)		22.6 ± .812 (5)		23.6 ± .600 (5)		23.8 ± .916 (5)	
WEEK 1		22.5 ± .438 (20)	22.8 ± 1.07 (5)		23.2 ± 1.24 (5)		23.0 ± 1.18 (5)		19.6 ± .748 (5)	
WEEK 2		21.5 ± .520 (20)	20.4 ± .872 (5)		23.2 ± 1.24 (5)		21.8 ± .663 (5)		17.6 ± .980 (5)	*
WEEK 3		23.1 ± .715 (20)	24.2 ± 1.36 (5)		26.0 ± 1.41 (5)		24.4 ± .510 (5)		19.0 ± 1.00 (5)	
WEEK 4		24.5 ± .790 (20)	25.4 ± 1.60 (5)		26.4 ± 1.72 (5)		24.6 ± .600 (5)		21.0 ± 1.30 (5)	
WEEK 5		25.1 ± .899 (15)	27.8 ± 1.66 (5)		30.0 ± 1.87 (5)		26.0 ± .447 (5)		23.2 ± 1.07 (5)	
WEEK 6	*	25.9 ± 1.31 (15)	29.0 ± 1.76 (5)		30.6 ± 1.63 (5)	*	28.0 ± .707 (5)		25.4 ± .678 (5)	
WEEK 7		26.7 ± 1.12 (15)	30.0 ± 1.82 (5)		30.0 ± 1.30 (5)		27.8 ± 1.02 (5)		26.0 ± .775 (5)	
WEEK 8		26.7 ± 1.16 (14)	31.4 ± 1.86 (5)		32.4 ± 1.60 (5)		29.6 ± 1.25 (5)		27.2 ± .735 (5)	
WEEK 9		25.9 ± 1.30 (9)	31.0 ± 1.92 (5)		30.4 ± 1.75 (5)		27.2 ± 1.24 (5)		25.2 ± .860 (5)	
WEEK 10		25.0 ± 1.26 (9)	26.6 ± 1.60 (5)		31.4 ± 1.81 (5)	*	28.4 ± 1.21 (5)		27.2 ± .583 (5)	
WEEK 11		27.8 ± 1.36 (9)	34.8 ± 1.66 (5)	*	32.8 ± 1.85 (5)		31.2 ± 1.36 (5)		29.6 ± .600 (5)	
WEEK 12		26.8 ± 1.36 (9)	32.6 ± 1.75 (5)		32.0 ± 1.70 (5)		30.2 ± .860 (5)		28.8 ± .735 (5)	
WEEK 13		26.1 ± 1.55 (9)	33.2 ± 1.96 (5)		33.2 ± 1.83 (5)		30.8 ± 1.02 (5)		29.6 ± .927 (5)	
WEEK 14		27.7 ± 2.93 (4)	33.8 ± 1.91 (5)		32.6 ± 1.89 (5)		31.0 ± .894 (5)		29.8 ± .800 (5)	
WEEK 15		29.0 ± 2.80 (4)	35.2 ± 1.93 (5)		33.4 ± 1.75 (5)		31.2 ± 1.07 (5)		30.8 ± 1.02 (5)	
WEEK 16		29.2 ± 2.87 (4)	32.0 ± 1.76 (5)		33.2 ± 1.77 (5)		31.6 ± .927 (5)		30.8 ± .800 (5)	
WEEK 17		28.2 ± 2.87 (4)	33.2 ± 1.93 (5)		33.2 ± 1.71 (5)		31.0 ± .837 (5)		31.8 ± 1.07 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 125

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF MALE MICE AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
WEEK 1		1.50 ± .793 (20)	2.20 ± 1.16 (5)	•	-1.00 ± .633 (5)	•	-1.20 ± 1.96 (5)	•	-1.60 ± 1.21 (5)	•
WEEK 2		-.50 ± .420 (20)	1.60 ± .927 (5)		-2.00 ± .707 (4)		3.00 ± .913 (4)	*	-1.40 ± .812 (5)	
WEEK 3		1.60 ± .419 (20)	2.40 ± .678 (5)		3.00 ± 1.22 (4)		3.00 ± 1.08 (4)		4.20 ± .860 (5)	
WEEK 4		2.15 ± .274 (20)	1.00 ± .316 (5)		2.00 ± .408 (4)		2.50 ± .289 (4)		3.60 ± .748 (5)	
WEEK 5		2.27 ± .521 (15)	-1.20 ± 1.46 (5)	D	2.50 ± .866 (4)		2.00 ± .408 (4)		2.80 ± .583 (5)	
WEEK 6		1.67 ± .599 (15)	3.40 ± .927 (5)		.50 ± .500 (4)		-.25 ± .854 (4)		2.80 ± .490 (5)	
WEEK 7		-.33 ± .319 (15)	1.60 ± 1.21 (5)		.50 ± .500 (4)	•	1.25 ± .479 (4)	•	2.60 ± .600 (5)	*
WEEK 8	+	3.00 ± 1.32 (15)	-1.20 ± .800 (5)	* D	2.00 ± .577 (4)		2.25 ± .479 (4)		.40 ± .245 (5)	D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 126

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF FEMALE MICE AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
WEEK 1		-.65 ± .393 (20)	2.20 ± .374 (5)	•	1.60 ± .927 (5)	•	-1.40 ± 1.03 (5)	•	-5.00 ± .548 (5)	+ •
WEEK 2		-1.05 ± .461 (20)	.60 ± .678 (5)	•	-1.00 ± 1.34 (5)	•	2.20 ± .583 (5)	•	2.20 ± .735 (5)	•
WEEK 3		1.70 ± .385 (20)	2.00 ± .548 (5)		2.60 ± .400 (5)		2.20 ± .583 (5)		3.20 ± .800 (5)	
WEEK 4		1.30 ± .263 (20)	.60 ± .400 (5)		.40 ± .400 (5)		1.80 ± .374 (5)		2.00 ± .316 (5)	
WEEK 5		1.27 ± .431 (15)	1.00 ± .548 (5)		-5.40 ± .510 (5)	+ D	.40 ± 1.21 (5)		.40 ± .872 (5)	
WEEK 6	*	.73 ± .628 (15)	.80 ± .374 (5)	•	6.80 ± .200 (5)	+ •	0.00 ± 1.05 (5)	•	1.40 ± .400 (5)	•
WEEK 7	+	.87 ± .827 (15)	1.20 ± .374 (5)	•	1.40 ± .510 (5)	•	.80 ± .374 (5)	•	2.20 ± .200 (5)	•
WEEK 8		.07 ± .267 (14)	-1.20 ± .374 (5)	•	2.60 ± .400 (5)	+ •	2.20 ± .374 (5)	+ •	1.20 ± .490 (5)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 127

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF MALE MICE AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T	R	.005 % IN DIET	T	R	.025 % IN DIET	T	R	.125 % IN DIET	T	R
WEEK 1		1.50 ± .793 (20)	2.60 ± 1.81 (5)		•	1.00 ± 1.52 (5)		•	-.20 ± 1.88 (5)		•	-3.20 ± 1.32 (5)		•
WEEK 2		-.50 ± .420 (20)	-.60 ± .812 (5)		•	.80 ± .533 (5)		•	1.40 ± .980 (5)			.40 ± .400 (5)		•
WEEK 3	*	1.60 ± .419 (20)	3.40 ± .510 (5)	*		1.60 ± .678 (5)			1.60 ± 1.54 (5)			4.40 ± .245 (5)	+	A
WEEK 4	*	2.15 ± .274 (20)	-.40 ± .510 (5)	*	D	-2.00 ± 1.79 (5)			.60 ± .927 (5)			1.20 ± .374 (5)		
WEEK 5		2.27 ± .521 (15)	3.60 ± 1.21 (5)			2.40 ± 1.12 (5)			1.00 ± 1.14 (5)			2.00 ± .316 (5)		
WEEK 6		1.67 ± .599 (15)	2.40 ± .510 (5)			0.00 ± .633 (5)			3.00 ± 1.41 (4)			2.20 ± .374 (5)		
WEEK 7		-.33 ± .319 (15)	.80 ± .374 (5)		•	1.40 ± .245 (5)			2.00 ± .577 (4)	*		3.00 ± .548 (5)	+	
WEEK 8	+	3.00 ± 1.32 (15)	1.00 ± .633 (5)		A	1.00 ± .447 (5)		B	2.00 ± 0.00 (4)			1.80 ± .374 (5)		
WEEK 9		-.70 ± .367 (10)	-1.20 ± .583 (5)		•	-1.40 ± .400 (5)		•	-.50 ± .289 (4)		•	-1.00 ± .949 (5)		•
WEEK 10		.70 ± .495 (10)	3.20 ± .200 (5)	*	•	.20 ± .663 (5)		•	.75 ± .479 (4)		•	-1.00 ± .707 (5)		•
WEEK 11		2.20 ± .573 (10)	1.60 ± .510 (5)			2.80 ± .970 (5)			1.50 ± .645 (4)			3.80 ± .374 (5)		
WEEK 12		-1.00 ± .365 (10)	-.60 ± .748 (5)		•	-1.20 ± .490 (5)		•	-1.00 ± .617 (4)		•	-3.60 ± .510 (5)	*	•
WEEK 13	*	.40 ± .718 (10)	.40 ± .510 (5)		•	1.25 ± 1.25 (4)		•	3.25 ± .250 (4)	*	•	2.60 ± .245 (5)	*	•
WEEK 14		.60 ± .678 (5)	-.20 ± .374 (5)		•	-.75 ± .750 (4)		•	-1.50 ± .289 (4)		•	1.80 ± .490 (5)		•
WEEK 15		2.00 ± .633 (5)	2.40 ± .678 (5)			1.75 ± .479 (4)			.75 ± .479 (4)			4.20 ± .583 (5)		
WEEK 16		-.20 ± .663 (5)	-.80 ± .490 (5)		•	2.25 ± 1.25 (4)			.25 ± .854 (4)		•	-1.00 ± .707 (5)		•
WEEK 17	*	-1.60 ± 1.75 (5)	-1.40 ± .400 (5)		D	-2.50 ± 1.44 (4)		•	-.75 ± .250 (4)		•	-.60 ± .980 (5)		•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 128

EFFECTS OF TNT ON WEEKLY INCREASES IN BODY WEIGHT (G)
OF FEMALE MICE AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
WEEK 1		-.65 ± .393 (20)	.20 ± 1.24 (5)	•	.60 ± .510 (5)	•	-.60 ± 1.36 (5)	•	-4.20 ± 1.56 (5)	
WEEK 2		-1.05 ± .461 (20)	-2.40 ± .872 (5)	•	0.00 ± 0.00 (5)	•	-1.20 ± .970 (5)	•	-2.00 ± .894 (5)	•
WEEK 3		1.70 ± .385 (20)	3.80 ± .490 (5)		2.80 ± .374 (5)		2.60 ± .510 (5)		1.40 ± .245 (5)	
WEEK 4		1.30 ± .263 (20)	1.20 ± .583 (5)		.40 ± .400 (5)		.20 ± .200 (5)		2.00 ± .447 (5)	
WEEK 5	*	1.27 ± .431 (15)	2.40 ± .245 (5)	*	3.60 ± .245 (5)	+	1.40 ± .245 (5)		2.20 ± .374 (5)	
WEEK 6		.73 ± .628 (15)	1.20 ± .490 (5)	•	.60 ± 1.17 (5)	•	2.00 ± .447 (5)	•	2.20 ± .583 (5)	•
WEEK 7	*	.87 ± .827 (15)	1.00 ± .633 (5)	•	-.60 ± 1.17 (5)	•	-.20 ± .583 (5)	•	.60 ± .245 (5)	•
WEEK 8		.07 ± .267 (14)	1.40 ± .245 (5)	•	2.40 ± .400 (5)	+ •	1.80 ± .490 (5)	* •	1.20 ± .200 (5)	•
WEEK 9		1.33 ± .441 (9)	-.40 ± .600 (5)	D	-2.00 ± .316 (5)	+ D	-2.40 ± .400 (5)	+ D	-2.00 ± .316 (5)	+ D
WEEK 10		-.89 ± .588 (9)	-4.40 ± .510 (5)	+ •	1.00 ± .316 (5)	•	1.20 ± .200 (5)	•	2.00 ± .707 (5)	* •
WEEK 11	*	2.78 ± .547 (9)	8.20 ± .374 (5)	+ C	1.40 ± .245 (5)	* A	2.80 ± .200 (5)		2.40 ± .400 (5)	
WEEK 12		-1.00 ± .333 (9)	-2.20 ± .374 (5)	•	-.80 ± .374 (5)	•	-1.00 ± .548 (5)	•	-.80 ± .490 (5)	•
WEEK 13		-.67 ± .500 (9)	.60 ± .510 (5)	•	1.20 ± .583 (5)	•	.60 ± .245 (5)	•	.80 ± .374 (5)	•
WEEK 14		0.00 ± .408 (4)	.60 ± .400 (5)	•	-.60 ± .510 (5)	•	.20 ± .490 (5)	•	.20 ± .374 (5)	•
WEEK 15		1.25 ± .250 (4)	1.40 ± .400 (5)		.80 ± .583 (5)		.20 ± .374 (5)	A	1.00 ± .447 (5)	
WEEK 16		.25 ± .479 (4)	-3.20 ± .374 (5)	+ •	-.20 ± .490 (5)	•	.40 ± .245 (5)	•	0.00 ± .447 (5)	•
WEEK 17		-1.00 ± 0.00 (4)	1.20 ± .200 (5)	•	0.00 ± .707 (5)	•	-.60 ± .510 (5)	•	1.00 ± .316 (5)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 129

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .001 % IN DIET	W	.005 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	2.8 ± .204	(4)	2.7 ± .275	(4)	2.6 ± .461	(4)	2.4 ± .186	(4)	2.2 ± .264	(4)
WEEK 2	3.3 ± .196	(4)	3.4 ± .337	(4)	3.2 ± .475	(4)	3.4 ± .314	(4)	2.9 ± .381	(4)
WEEK 3	4.1 ± .357	(4)	4.4 ± .332	(4)	4.0 ± .479	(4)	4.0 ± .400	(4)	4.5 ± .148	(4)
WEEK 4	4.7 ± .355	(4)	4.3 ± .197	(4)	3.9 ± .472	(4)	4.2 ± .450	([illegible])	4.2 ± .176	(4)
WEEK 5	4.6 ± .597	(3)	4.9 ± .343	(2)	4.7 ± 1.26	(2)	3.3 ± .100	(2)	4.6 ± .224	(2)
WEEK 6	5.3 ± .184	(3)	5.0 ± .214	(2)	4.7 ± .971	(2)	3.7 ± .343	(2)	4.9 ± .135	(2)
WEEK 7	4.9 ± .247	(3)	5.0 ± .157	(2)	4.8 ± .886	(2)	4.5 ± .153	(2)	5.2 ± .135	(2)
WEEK 8	5.2 ± .497	(3)	5.2 ± .357	(2)	4.8 ± 1.04	(2)	4.5 ± .071	(2)	5.2 ± .280	(2)
WEEK 9	4.8 ± .357	(2)	5.0 ± .214	(2)	4.7 ± 1.06	(2)	4.4 ± .110	(2)	5.0 ± .401	(2)
WEEK 10	4.6 ± .200	(2)	6.1 ± .086	(2)	4.6 ± 1.09	(2)	4.3 ± .075	(2)	4.3 ± .774	(2)
WEEK 11	4.9 ± .47[illegible]	(2)	5.6 ± .157	(2)	5.4 ± .714	(2)	4.8 ± .089	(2)	5.5 ± .060	(2)
WEEK 12	5.2 ± .157	(2)	5.5 ± .071	(2)	5.2 ± .986	(2)	4.7 ± .032	(2)	5.2 ± .419	(2)
WEEK 13	5.9 ± .017	(2)	6.4 ± 1.11	(2)	6.4 ± 1.5[illegible]	(2)	5.1 ± .064	(2)	6.0 ± .607	(2)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 130

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	W	.005 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	2.8 ± .066 (4)	2.8 ± .183 (4)		3.6 ± .155 (4)		2.3 ± .233 (4)		2.0 ± .108 (4)	
WEEK 2	2.7 ± .309 (4)	2.9 ± .258 (4)		3.5 ± .251 (4)		3.0 ± .220 (4)		2.3 ± .125 (4)	
WEEK 3	3.4 ± .454 (4)	4.4 ± .076 (4)		4.0 ± .217 (4)		4.1 ± .105 (4)		3.8 ± .356 (4)	
WEEK 4	4.0 ± .552 (4)	4.5 ± .179 (4)		4.4 ± .105 (4)		4.2 ± .228 (4)		4.0 ± .250 (4)	
WEEK 5	3.5 ± .425 (3)	4.9 ± .343 (2)		4.9 ± .229 (2)		4.5 ± .200 (2)		3.8 ± .243 (2)	
WEEK 6	3.8 ± .629 (3)	4.9 ± .071 (2)		5.0 ± .043 (2)		4.4 ± .071 (2)		3.0 ± 1.53 (2)	
WEEK 7	4.1 ± .615 (3)	4.6 ± .086 (2)		5.0 ± .243 (2)		4.4 ± .243 (2)		4.4 ± .257 (2)	
WEEK 8	4.1 ± .724 (3)	5.0 ± .229 (2)		5.3 ± .229 (2)		4.7 ± .314 (2)		4.3 ± .371 (2)	
WEEK 9	3.5 ± .376 (2)	4.7 ± .[illegible]4 (2)		4.7 ± .043 (2)		4.0 ± .043 (2)		4.2 ± .371 (2)	
WEEK 10	3.0 ± .142 (2)	4.0 ± .957 (2)		4.5 ± .571 (2)		4.4 ± .029 (2)		3.9 ± .286 (2)	
WEEK 11	4.0 ± .522 (2)	5.8 ± .186 (2)		5.7 ± .329 (2)		5.4 ± .414 (2)		4.8 ± .300 (2)	
WEEK 12	3.7 ± .284 (2)	5.0 ± .143 (2)		5.5 ± .343 (2)		4.8 ± .271 (2)		4.6 ± .414 (2)	
WEEK 13	4.2 ± .086 (2)	5.8 ± 1.09 (2)		5.6 ± .218 (2)		5.1 ± .439 (2)		5.2 ± .805 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 131

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE MICE DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

		TREATMENT GROUPS							
DEPENDENT VARIABLE	CONTROL GROUP	.001 % IN DIET	W	.005 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	2.8 ± .204 (4)	2.9 ± 0.00 (1)		1.7 ± 0.00 (1)		2.6 ± 0.00 (1)		2.9 ± 0.00 (1)	
WEEK 2	3.3 ± .196 (4)	3.8 ± 0.00 (1)		2.2 ± 0.00 (1)		4.1 ± 0.00 (1)		2.3 ± 0.00 (1)	
WEEK 3	4.1 ± .357 (4)	4.7 ± 0.00 (1)		3.4 ± 0.00 (1)		4.9 ± 0.00 (1)		4.3 ± 0.00 (1)	
WEEK 4	4.7 ± .355 (4)	4.7 ± 0.00 (1)		3.8 ± 0.00 (1)		5.2 ± 0.00 (1)		4.2 ± 0.00 (1)	
WEEK 5	4.6 ± .597 (3)	4.1 ± 0.00 (1)		4.0 ± 0.00 (1)		5.3 ± 0.00 (1)		5.3 ± 0.00 (1)	
WEEK 6	5.3 ± .184 (3)	5.2 ± 0.00 (1)		4.6 ± 0.00 (1)		6.0 ± 0.00 (1)		5.7 ± 0.00 (1)	
WEEK 7	4.9 ± .247 (3)	5.0 ± 0.00 (1)		4.9 ± 0.00 (1)		5.8 ± 0.00 (1)		5.3 ± 0.00 (1)	
WEEK 8	5.2 ± .497 (3)	4.8 ± 0.00 (1)		4.6 ± 0.00 (1)		5.9 ± 0.00 (1)		5.5 ± 0.00 (1)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 132

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE MICE DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	W	.065 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	2.8 ± .066 (4)	3.2 ± 0.00 (1)		3.6 ± 0.00 (1)		2.6 ± 0.00 (1)		2.0 ± 0.00 (1)	
WEEK 2	2.7 ± .309 (4)	3.5 ± 0.00 (1)		3.2 ± 0.00 (1)		3.6 ± 0.00 (1)		2.4 ± 0.[illegible] (1)	
WEEK 3	3.4 ± .454 (4)	4.6 ± 0.00 (1)		4.2 ± 0.00 (1)		4.3 ± 0.00 (1)		4.7 ± 0.00 (1)	
WEEK 4	4.0 ± .552 (4)	4.2 ± 0.0[illegible] [illegible]		4.3 ± 0.00 (1)		4.8 ± 0.00 (1)		4.3 ± 0.00 (1)	
WEEK 5	3.5 ± .425 (3)	4.5 ± [illegible].00 (1)		3.4 ± 0.00 (1)		4.4 ± 0.00 (1)		4.7 ± 0.00 (1)	
WEEK 6	3.8 ± .629 (3)	4.9 ± 0.00 (1)		5.5 ± 0.00 (1)		4.5 ± 0.00 (1)		4.9 ± 0.00 (1)	
WEEK 7	4.1 ± .615 (3)	4.9 ± 0.00 (1)		5.1 ± 0.00 (1)		5.1 ± 0.00 (1)		5.1 ± 0.00 (1)	
WEEK 8	4.1 ± .724 (3)	5.0 ± 0.00 (1)		4.9 ± 0.00 (1)		5.1 ± 0.00 (1)		5.2 ± 0.00 (1)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 133

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE MICE DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .001 % IN DIET		W	.005 % IN DIET		W	.025 % IN DIET		W	.125 % IN DIET		W
WEEK 1	2.8 ± .204	(4)	2.8 ± 0.00	(1)		2.7 ± 0.00	(1)		1.9 ± 0.00	(1)		1.8 ± 0.00	(1)	
WEEK 2	3.3 ± .196	(4)	3.3 ± 0.00	(1)		3.7 ± 0.00	(1)		3.1 ± 0.00	(1)		2.3 ± 0.00	(1)	
WEEK 3	4.1 ± .357	(4)	4.6 ± 0.00	(1)		3.9 ± 0.00	(1)		3.2 ± 0.00	(1)		4.2 ± 0.00	(1)	
WEEK 4	4.7 ± .355	(4)	4.0 ± 0.00	(1)		3.1 ± 0.00	(1)		3.4 ± 0.00	(1)		3.8 ± 0.00	(1)	
WEEK 5	4.6 ± .597	(3)	4.6 ± 0.00	(1)		3.5 ± 0.00	(1)		3.2 ± 0.00	(1)		4.4 ± 0.00	(1)	
WEEK 6	5.3 ± .184	(3)	4.8 ± 0.00	(1)		3.8 ± 0.00	(1)		3.4 ± 0.00	(1)		4.8 ± 0.00	(1)	
WEEK 7	4.9 ± .247	(3)	4.8 ± 0.00	(1)		3.9 ± 0.00	(1)		4.7 ± 0.00	(1)		5.1 ± 0.00	(1)	
WEEK 8	5.2 ± .497	(3)	4.8 ± 0.00	(1)		3.8 ± 0.00	(1)		4.6 ± 0.00	(1)		5.0 ± 0.00	(1)	
WEEK 9	4.8 ± .357	(2)	4.8 ± 0.00	(1)		3.7 ± 0.00	(1)		4.3 ± 0.00	(1)		4.7 ± 0.00	(1)	
WEEK 10	4.6 ± .200	(2)	6.1 ± 0.00	(1)		3.5 ± 0.00	(1)		4.3 ± 0.00	(1)		3.7 ± 0.00	(1)	
WEEK 11	4.9 ± .471	(2)	5.5 ± 0.00	(1)		4.7 ± 0.00	(1)		4.9 ± 0.00	(1)		5.5 ± 0.00	(1)	
WEEK 12	5.2 ± .157	(2)	5.5 ± 0.00	(1)		4.2 ± 0.00	(1)		4.8 ± 0.00	(1)		4.8 ± 0.00	(1)	
WEEK 13	5.9 ± .017	(2)	5.4 ± 0.00	(1)		5.0 ± 0.00	(1)		5.1 ± 0.00	(1)		5.5 ± 0.00	(1)	
WEEK 14	5.5 ± 0.00	(1)	5.4 ± 0.00	(1)		5.3 ± 0.00	(1)		4.7 ± 0.00	(1)		5.9 ± 0.00	(1)	
WEEK 15	5.6 ± 0.00	(1)	5.4 ± 0.00	(1)		4.9 ± 0.00	(1)		4.8 ± 0.00	(1)		5.7 ± 0.00	(1)	
WEEK 16	5.2 ± 0.00	(1)	5.1 ± 0.00	(1)		4.5 ± 0.00	(1)		4.8 ± 0.00	(1)		5.3 ± 0.00	(1)	
WEEK 17	5.0 ± 0.00	(1)	5.6 ± 0.00	(1)		5.4 ± 0.00	(1)		5.7 ± 0.00	(1)		6.1 ± 0.00	(1)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 134

EFFECTS OF TNT ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE MICE DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	W	.005 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	2.8 ± .066 (4)	2.4 ± 0.00 (1)		3.3 ± 0.00 (1)		2.7 ± 0.00 (1)		1.8 ± 0.00 (1)	
WEEK 2	2.7 ± .309 (4)	2.4 ± 0.00 (1)		3.6 ± 0.00 (1)		2.8 ± 0.00 (1)		2.0 ± 0.00 (1)	
WEEK 3	3.4 ± .454 (4)	4.3 ± 0.00 (1)		4.5 ± 0.00 (1)		3.8 ± 0.00 (1)		3.0 ± 0.00 (1)	
WEEK 4	4.0 ± .552 (4)	4.4 ± 0.00 (1)		4.5 ± 0.00 (1)		3.7 ± 0.00 (1)		3.6 ± 0.00 (1)	
WEEK 5	3.5 ± .425 (3)	4.5 ± 0.00 (1)		5.1 ± 0.00 (1)		4.3 ± 0.00 (1)		3.5 ± 0.00 (1)	
WEEK 6	3.8 ± .629 (3)	5.0 ± 0.00 (1)		4.9 ± 0.00 (1)		4.3 ± 0.00 (1)		1.4 ± 0.00 (1)	
WEEK 7	4.1 ± .615 (3)	4.5 ± 0.00 (1)		5.3 ± 0.00 (1)		4.1 ± 0.00 (1)		4.1 ± 0.00 (1)	
WEEK 8	4.1 ± .724 (3)	4.8 ± 0.00 (1)		5.5 ± 0.00 (1)		4.4 ± 0.00 (1)		3.9 ± 0.00 (1)	
WEEK 9	3.5 ± .376 (2)	4.7 ± 0.00 (1)		4.7 ± 0.00 (1)		3.9 ± 0.00 (1)		3.9 ± 0.00 (1)	
WEEK 10	3.0 ± .142 (2)	3.0 ± 0.00 (1)		4.0 ± 0.00 (1)		4.4 ± 0.00 (1)		3.6 ± 0.00 (1)	
WEEK 11	4.0 ± .522 (2)	6.0 ± 0.00 (1)		6.1 ± 0.00 (1)		4.9 ± 0.00 (1)		4.5 ± 0.00 (1)	
WEEK 12	3.7 ± .284 (2)	5.2 ± 0.00 (1)		5.8 ± 0.00 (1)		4.5 ± 0.00 (1)		4.1 ± 0.00 (1)	
WEEK 13	4.2 ± .086 (2)	4.8 ± 0.00 (1)		5.4 ± 0.00 (1)		4.7 ± 0.00 (1)		4.5 ± 0.00 (1)	
WEEK 14	4.1 ± 0.00 (1)	5.3 ± 0.00 (1)		5.7 ± 0.00 (1)		4.7 ± 0.00 (1)		4.9 ± 0.00 (1)	
WEEK 15	3.8 ± 0.00 (1)	4.9 ± 0.00 (1)		5.0 ± 0.00 (1)		4.5 ± 0.00 (1)		4.3 ± 0.00 (1)	
WEEK 16	3.5 ± 0.00 (1)	3.6 ± 0.00 (1)		4.9 ± 0.00 (1)		4.4 ± 0.00 (1)		4.2 ± 0.00 (1)	
WEEK 17	4.1 ± 0.00 (1)	5.3 ± 0.00 (1)		6.1 ± 0.00 (1)		1.3 ± 0.00 (1)		4.7 ± 0.00 (1)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 135

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF MALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	W	.005 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	117.3 ± 5.51 (4)	119.0 ± 7.31 (4)		112.9 ± 15.4 (4)		109.7 ± 3.92 (4)		109.9 ± 10.6 (4)	
WEEK 2	142.9 ± 5.80 (4)	147.1 ± 8.74 (4)		140.7 ± 12.7 (4)		144.9 ± 3.26 (4)		142.1 ± 13.0 (4)	
WEEK 3	165.8 ± 11.4 (4)	169.1 ± 5.94 (4)		155.1 ± 10.7 (4)		155.7 ± 5.13 (4)		178.7 ± 3.20 (4)	
WEEK 4	172.3 ± 11.9 (4)	163.9 ± 4.27 (4)		148.1 ± 9.35 (4)		154.8 ± 3.39 (4)		159.2 ± 1.13 (4)	
WEEK 5	153.8 ± 14.7 (3)	159.9 ± 6.48 (2)		156.0 ± 26.0 (2)		134.7 ± 1.32 (2)		160.2 ± 7.45 (2)	
WEEK 6	167.9 ± 3.37 (3)	161.7 ± 12.5 (2)		153.5 ± 11.7 (2)		135.9 ± 15.6 (2)		164.3 ± 5.23 (2)	
WEEK 7	156.6 ± 7.81 (3)	152.5 ± 6.20 (2)		153.5 ± 12.6 (2)		155.5 ± 1.91 (2)		162.7 ± .801 (2)	
WEEK 8	152.1 ± 11.0 (3)	152.0 ± 10.0 (2)		149.2 ± 19.1 (2)		145.1 ± 3.95 (2)		156.1 ± 7.10 (2)	
WEEK 9	149.0 ± 9.79 (2)	150.5 ± 4.17 (2)		147.8 ± 15.3 (2)		144.1 ± 8.14 (2)		152.3 ± 8.58 (2)	
WEEK 10	140.3 ± 7.00 (2)	168.8 ± .500 (2)		137.0 ± 9.54 (2)		136.5 ± 6.04 (2)		131.3 ± 15.8 (2)	
WEEK 11	141.6 ± 12.7 (2)	148.5 ± 2.57 (2)		153.3 ± 1.13 (2)		142.4 ± .428 (2)		155.8 ± 1.02 (2)	
WEEK 12	153.5 ± 6.47 (2)	152.5 ± 2.68 (2)		153.5 ± 11.6 (2)		143.8 ± 876 (2)		153.2 ± .338 (2)	
WEEK 13	171.6 ± 8.47 (2)	178.8 ± 39.8 (2)		179.2 ± 31.7 (2)		154.4 ± 14.9 (2)		182.0 ± 23.9 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 136

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF FEMALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .001 % IN DIET		W	.005 % IN DIET		W	.025 % IN DIET		W	.125 % IN DIET		W
WEEK 1	123.8 ± 2.14	(4)	121.7 ± 6.66	(4)		149.3 ± 2.65	(4)		108.6 ± 6.54	(4)		105.4 ± 5.36	(4)	
WEEK 2	123.9 ± 9.39	(4)	128.9 ± 5.76	(4)		147.5 ± 5.35	(4)		138.8 ± 5.54	(4)		120.9 ± 3.12	(4)	
WEEK 3	146.9 ± 10.8	(4)	175.3 ± 2.52	(4)		154.7 ± 9.19	(4)		165.5 ± 3.16	(4)		171.0 ± 9.25	(4)	
WEEK 4	161.3 ± 14.7	(4)	175.2 ± 11.2	(4)		166.6 ± 5.36	(4)		161.6 ± 5.05	(4)		168.9 ± 3.73	(4)	
WEEK 5	138.2 ± 8.39	(3)	171.2 ± 7.82	(2)		165.4 ± 6.03	(2)		161.6 ± 2.12	(2)		154.4 ± 1.72	(2)	
WEEK 6	144.0 ± 10.3	(3)	168.8 ± 3.60	(2)		166.3 ± 4.75	(2)		154.4 ± .340	(2)		110.0 ± 53.7	(2)	
WEEK 7	149.9 ± 11.4	(3)	155.3 ± 3.92	(2)		170.3 ± 5.90	(2)		148.7 ± .677	(2)		160.6 ± 2.37	(2)	
WEEK 8	151.0 ± 15.5	(3)	158.6 ± 5.71	(2)		163.5 ± 7.54	(2)		152.0 ± 4.28	(2)		150.1 ± 7.29	(2)	
WEEK 9	135.2 ± 10.4	(2)	150.2 ± .942	(2)		154.5 ± .391	(2)		141.5 ± 3.50	(2)		155.3 ± 2.24	(2)	
WEEK 10	[illegible]9.5 ± 7.85	(2)	131.8 ± 19.0	(2)		140.3 ± 13.8	(2)		150.8 ± 5.11	(2)		135.7 ± 3.35	(2)	
WEEK 11	141.9 ± 15.4	(2)	172.3 ± .903	(2)		171.7 ± 12.9	(2)		166.1 ± 7.71	(2)		155.7 ± 4.19	(2)	
WEEK 12	137.5 ± 9.57	(2)	154.7 ± 3.92	(2)		169.0 ± 13.1	(2)		150.5 ± 1.92	(2)		150.6 ± 6.74	(2)	
WEEK 13	159.6 ± 12.3	(2)	180.7 ± 41.7	(2)		175.4 ± 12.8	(2)		166.4 ± 15.4	(2)		176.7 ± 27.2	(2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 137

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF MALE MICE DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .001 % IN DIET	W	.005 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	117.3 ± 5.51	(4)	127.7 ± 0.00	(1)	80.1 ± 0.00	(1)	117.3 ± 0.00	(1)	138.7 ± 0.00	(1)
WEEK 2	142.9 ± 5.80	(4)	155.8 ± 0.00	(1)	109.9 ± 0.00	(1)	151.4 ± 0.00	(1)	120.5 ± 0.00	(1)
WEEK 3	165.8 ± 11.4	(4)	178.3 ± 0.00	(1)	150.7 ± 0.00	(1)	160.6 ± 0.00	(1)	183.2 ± 0.00	(1)
WEEK 4	172.3 ± 11.9	(4)	171.8 ± 0.00	(1)	151.5 ± 0.00	(1)	158.1 ± 0.00	(1)	156.6 ± 0.00	(1)
WEEK 5	153.8 ± 14.7	(3)	154.8 ± 0.00	(1)	145.5 ± 0.00	(1)	153.1 ± 0.00	(1)	179.3 ± 0.00	(1)
WEEK 6	167.9 ± 3.37	(3)	174.5 ± 0.00	(1)	164.7 ± 0.00	(1)	173.9 ± 0.00	(1)	173.5 ± 0.00	(1)
WEEK 7	156.6 ± 7.81	(3)	160.1 ± 0.00	(1)	171.9 ± 0.00	(1)	160.8 ± 0.00	(1)	150.2 ± 0.00	(1)
WEEK 8	152.1 ± 11.0	(3)	160.0 ± 0.00	(1)	152.3 ± 0.00	(1)	154.1 ± 0.00	(1)	154.1 ± 0.00	(1)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 138

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF FEMALE MICE DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .001 % IN DIET	W	.005 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	123.8 ± 2.14	(4)	135.7 ± 0.00	(1)	151.2 ± 0.00	(1)	120.2 ± 0.00	(1)	109.9 ± 0.00	(1)
WEEK 2	123.9 ± 9.39	(4)	144.0 ± 0.00	(1)	139.1 ± 0.00	(1)	153.8 ± 0.00	(1)	117.6 ± 0.00	(1)
WEEK 3	146.9 ± 10.8	(4)	174.2 ± 0.00	(1)	164.1 ± 0.00	(1)	168.3 ± 0.00	(1)	197.3 ± 0.00	(1)
WEEK 4	161.3 ± 14.7	(4)	156.6 ± 0.00	(1)	164.8 ± 0.00	(1)	172.9 ± 0.00	(1)	169.6 ± 0.00	(1)
WEEK 5	138.2 ± 8.39	(3)	161.2 ± 0.00	(1)	166.4 ± 0.00	(1)	156.1 ± 0.00	(1)	181.3 ± 0.00	(1)
WEEK 6	144.0 ± 10.3	(3)	168.7 ± 0.00	(1)	202.3 ± 0.00	(1)	159.2 ± 0.00	(1)	180.4 ± 0.00	(1)
WEEK 7	149.9 ± 11.4	(3)	164.8 ± 0.00	(1)	177.6 ± 0.00	(1)	177.6 ± 0.00	(1)	172.8 ± 0.00	(1)
WEEK 8	151.0 ± 15.5	(3)	174.8 ± 0.00	(1)	157.4 ± 0.00	(1)	164.1 ± 0.00	(1)	167.9 ± 0.00	(1)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 139

EFFECTS OF TNT ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF MALE MICE DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS .001 % IN DIET	W	.005 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	117.3 ± 5.51	(4)	116.4 ± 0.00	(1)	111.6 ± 0.00	(1)	99.1 ± 0.00	(1)	97.3 ± 0.00	(1)
WEEK 2	142.9 ± 5.80	(4)	141.6 ± 0.00	(1)	152.1 ± 0.00	(1)	145.6 ± 0.00	(1)	124.4 ± 0.00	(1)
WEEK 3	165.8 ± 11.4	(4)	171.9 ± 0.00	(1)	147.2 ± 0.00	(1)	142.9 ± 0.00	(1)	182.6 ± 0.00	(1)
WEEK 4	172.3 ± 11.9	(4)	152.7 ± 0.00	(1)	127.5 ± 0.00	(1)	147.8 ± 0.00	(1)	158.[illegible] ± 0.00	(1)
WEEK 5	153.8 ± 14.7	(3)	15[illegible].4 ± 0.00	(1)	130.0 ± 0.00	(1)	133.4 ± 0.00	(1)	166.8 ± 0.00	(1)
WEEK 6	167.9 ± 3.37	(3)	149.1 ± 0.00	(1)	141.8 ± 0.00	(1)	119.3 ± 0.00	(1)	169.0 ± 0.00	(1)
WEEK 7	156.6 ± 7.81	(3)	146.3 ± 0.00	(1)	140.8 ± 0.00	(1)	153.4 ± 0.00	(1)	162.0 ± 0.00	(1)
WEEK 8	152.1 ± 11.0	(3)	142.0 ± 0.00	(1)	130.0 ± 0.00	(1)	140.7 ± 0.00	(1)	149.7 ± 0.00	(1)
WEEK 9	149.0 ± 9.79	(2)	146.3 ± 0.00	(1)	132.5 ± 0.00	(1)	135.0 ± 0.00	(1)	144.6 ± 0.00	(1)
WEEK 10	140.3 ± 7.00	(2)	168.3 ± 0.00	(1)	127.4 ± 0.00	(1)	129.8 ± 0.00	(1)	117.2 ± 0.00	(1)
WEEK 11	141.6 ± 12.7	(2)	145.9 ± 0.00	(1)	152.2 ± 0.00	(1)	142.9 ± 0.00	(1)	156.7 ± 0.00	(1)
WEEK 12	153.5 ± 6.47	(2)	149.8 ± 0.00	(1)	141.9 ± 0.00	(1)	142.9 ± 0.00	(1)	152.9 ± 0.00	(1)
WEEK 13	171.6 ± 8.47	(2)	145.1 ± 0.00	(1)	149.3 ± 0.00	(1)	138.9 ± 0.00	(1)	162.2 ± 0.00	(1)
WEEK 14	151.5 ± 0.00	(1)	145.9 ± 0.00	(1)	160.3 ± 0.00	(1)	134.7 ± 0.00	(1)	166.0 ± 0.00	(1)
WEEK 15	146.6 ± 0.00	(1)	137.1 ± 0.00	(1)	138.7 ± 0.00	(1)	133.9 ± 0.00	(1)	143.6 ± 0.00	(1)
WEEK 16	135.4 ± 0.00	(1)	131.1 ± 0.00	(1)	122.4 ± 0.00	(1)	132.9 ± 0.00	(1)	137.0 ± 0.00	(1)
WEEK 17	136.6 ± 0.00	(1)	148.7 ± 0.00	(1)	156.9 ± 0.00	(1)	160.8 ± 0.00	(1)	157.7 ± 0.00	(1)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

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EFFEC OF TNT ON . . CONSUMPTION /KG (BODY WT)/DAY)
OF FEMALE . DURING 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	W	.005 % IN DIET	W	.025 % IN DIET	W	.125 % IN DIET	W
WEEK 1	123.8 ± 2.14 (4)	104.0 ± 0.00	(1)	141.6 ± 0.00	(1)	116.8 ± 0.00	(1)	93.3 ± 0.00	(1)
WEEK 2	123.9 ± 9.39 (4)	116.2 ± 0.00	(1)	155.2 ± 0.00	(1)	128.4 ± 0.00	(1)	113.6 ± 0.00	(1)
WEEK 3	146.9 ± 10.8 (4)	178.3 ± 0.00	(1)	173.6 ± 0.00	(1)	156.9 ± 0.00	(1)	157.9 ± 0.00	(1)
WEEK 4	161.3 ± 14.7 (4)	173.2 ± 0.00	(1)	168.8 ± 0.00	(1)	149.8 ± 0.00	(1)	170.1 ± 0.00	(1)
WEEK 5	138.2 ± 8.39 (3)	163.4 ± 0.00	(1)	171.4 ± 0.00	(1)	163.7 ± 0.00	(1)	152.7 ± 0.00	(1)
WEEK 6	144.0 ± 10.3 (3)	172.4 ± 0.00	(1)	161.5 ± 0.00	(1)	154.1 ± 0.00	(1)	56.2 ± 0.00	(1)
WEEK 7	149.9 ± 11.4 (3)	151.4 ± 0.00	(1)	176.2 ± 0.00	(1)	148.0 ± 0.00	(1)	158.2 ± 0.00	(1)
WEEK 8	151.0 ± 15.5 (3)	152.9 ± 0.00	(1)	171.1 ± 0.00	(1)	147.7 ± 0.00	(1)	142.9 ± 0.00	(1)
WEEK 9	135.2 ± 10.4 (2)	151.2 ± 0.00	(1)	154.1 ± 0.00	(1)	145.0 ± 0.00	(1)	153.1 ± 0.00	(1)
WEEK 10	119.5 ± 7.85 (2)	112.8 ± 0.00	(1)	126.5 ± 0.00	(1)	155.9 ± 0.00	(1)	132.4 ± 0.00	(1)
WEEK 11	141.9 ± 15.4 (2)	173.2 ± 0.00	(1)	184.7 ± 0.00	(1)	158.4 ± 0.00	(1)	151.5 ± 0.00	(1)
WEEK 12	137.5 ± 9.57 (2)	158.6 ± 0.00	(1)	182.1 ± 0.00	(1)	148.5 ± 0.00	(1)	143.8 ± 0.00	(1)
WEEK 13	159.6 ± 12.3 (2)	145.4 ± 0.00	(1)	163.5 ± 0.00	(1)	152.1 ± 0.00	(1)	151.5 ± 0.00	(1)
WEEK 14	146.7 ± 0.00 (1)	156.4 ± 0.00	(1)	174.4 ± 0.00	(1)	153.0 ± 0.00	(1)	164.9 ± 0.00	(1)
WEEK 15	129.3 ± 0.00 (1)	138.0 ± 0.00	(1)	150.6 ± 0.00	(1)	143.8 ± 0.00	(1)	139.1 ± 0.00	(1)
WEEK 16	118.4 ± 0.00 (1)	113.4 ± 0.00	(1)	148.0 ± 0.00	(1)	138.3 ± 0.00	(1)	135.4 ± 0.00	(1)
WEEK 17	145.1 ± 0.00 (1)	160.2 ± 0.00	(1)	182.7 ± 0.00	(1)	41.9 ± 0.00	(1)	149.1 ± 0.00	(1)

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 141

DOSES OF TNT (MG/KG (BODY WT)/DAY) IN DIETS CONSUMED BY MALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS			
	.001 % IN DIET	.005 % IN DIET	.025 % IN DIET	.125 % IN DIET
WEEK 1	1.19	5.64	27.4	137.3
WEEK 2	1.47	7.03	36.2	177.6
WEEK 3	1.69	7.75	38.9	223.4
WEEK 4	1.64	7.41	38.7	199.0
WEEK 5	1.60	7.80	33.7	200.2
WEEK 6	1.62	7.67	34.0	205.4
WEEK 7	1.53	7.67	38.9	203.4
WEEK 8	1.52	7.46	36.3	195.1
WEEK 9	1.51	7.39	36.0	190.4
WEEK 10	1.69	6.85	34.1	164.2
WEEK 11	1.48	7.67	35.6	194.8
WEEK 12	1.52	7.68	36.0	191.5
WEEK 13	1.79	8.96	38.6	227.5

TABLE 142

DOSES OF TNT (MG/KG (BODY WT)/DAY) IN DIETS CONSUMED BY
FEMALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS			
	.001 % IN DIET	.005 % IN DIET	.025 % IN DIET	.125 % IN DIET
WEEK 1	1.22	7.46	27.2	131.7
WEEK 2	1.29	7.38	34.7	151.1
WEEK 3	1.75	7.74	41.4	213.8
WEEK 4	1.75	8.33	40.4	211.1
WEEK 5	1.71	8.27	40.4	193.0
WEEK 6	1.69	8.31	38.6	137.5
WEEK 7	1.55	8.51	37.2	200.8
WEEK 8	1.59	8.18	38.0	187.7
WEEK 9	1.50	7.73	35.4	194.1
WEEK 10	1.32	7.01	37.7	169.6
WEEK 11	1.72	8.59	41.5	194.7
WEEK 12	1.55	8.45	37.6	188.2
WEEK 13	1.81	8.77	41.6	220.9

TABLE 143

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE MICE AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS: .001 % IN DIET	T	R	.005 % IN DIET	T	R	.025 % IN DIET	T	R	.125 % IN DIET	T	R
FINAL WT (G)		25.60 ± 2.14 (5)	24.20 ± 1.11 (5)			26.00 ± .837 (5)			30.60 ± 2.50 (5)			28.60 ± 2.99 (5)		
BRAIN		.47 ± .013 (5)	.46 ± .008 (5)			.44 ± .008 (5)			.48 ± .016 (5)			.48 ± .022 (5)		
HEART	*	.16 ± .014 (5)	.12 ± .005 (5)			.12 ± .004 (5)			.12 ± .006 (5)			.14 ± .015 (5)		
KIDNEYS		.39 ± .030 (5)	.34 ± .012 (5)		A	.38 ± .030 (5)			.44 ± .038 (5)		A	.43 ± .052 (5)		
LIVER		1.51 ± .143 (5)	1.29 ± .064 (5)			1.47 ± .097 (5)			2.13 ± .182 (5)			1.77 ± .216 (5)		
SPLEEN	+	.07 ± .013 (5)	.12 ± .009 (5)	*		.10 ± .022 (5)			.09 ± .005 (5)			.18 ± .044 (5)		
TESTES		.33 ± .051 (5)	.24 ± .018 (5)		B	.29 ± .013 (5)		A	.34 ± .026 (5)			.32 ± .036 (5)		
BRAIN/BYWT		18.62 ± 1.22 (5)	18.92 ± .655 (5)			17.12 ± .515 (5)			15.82 ± .864 (5)			17.40 ± 1.79 (5)		
HEART/BYWT	+	6.13 ± .374 (5)	4.95 ± .044 (5)	*		4.64 ± .043 (5)	*		4.12 ± .216 (5)	*	A	4.92 ± .258 (5)	*	
KIDNEYS/BYWT		15.46 ± .794 (5)	13.91 ± .427 (5)			14.63 ± .798 (5)			14.48 ± .232 (5)			14.75 ± .772 (5)		
LIVER/BYWT		58.88 ± .924 (5)	53.56 ± 1.81 (5)			56.45 ± 2.55 (5)			69.63 ± 1.29 (5)	*		61.71 ± 2.18 (5)		
SPLEEN/BYWT	+	2.79 ± .284 (5)	5.14 ± .184 (5)	+	B	3.86 ± .698 (5)			3.08 ± .106 (5)			6.04 ± 1.09 (5)	*	
TESTES/BYWT		12.75 ± 1.08 (5)	9.74 ± .624 (5)			11.00 ± .403 (5)			11.17 ± .947 (5)			10.98 ± .346 (5)		
HEART/BRAIN	*	.33 ± .027 (5)	.26 ± .008 (5)			.27 ± .007 (5)			.26 ± .008 (5)			.29 ± .023 (5)		
KIDNEYS/BRAIN		.84 ± .056 (5)	.74 ± .019 (5)			.86 ± .057 (5)			.93 ± .057 (5)			.88 ± .092 (5)		
LIVER/BRAIN		3.22 ± .238 (5)	2.84 ± .094 (5)			3.32 ± .202 (5)			4.46 ± .267 (5)	*		3.69 ± .394 (5)		
SPLEEN/BRAIN	+	.16 ± .024 (5)	.27 ± .017 (5)	*		.23 ± .045 (5)			.20 ± .007 (5)			.37 ± .094 (5)		
TESTES/BRAIN		.70 ± .090 (5)	.52 ± .039 (5)			.65 ± .033 (5)			.71 ± .038 (5)			.66 ± .064 (5)		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 144

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE MICE AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
FINAL WT (G)		26.20 ± .663 (5)	24.00 ± .837 (5)		31.80 ± 1.24 (5)	*	28.00 ± 1.10 (5)		26.40 ± 1.50 (5)	
BRAIN		.48 ± .012 (5)	.48 ± .011 (5)		.51 ± .013 (5)		.51 ± .008 (5)		.52 ± .017 (5)	
HEART		.14 ± .007 (5)	.12 ± .005 (5)	A	.13 ± .004 (5)		.14 ± .010 (5)		.13 ± .007 (5)	
KIDNEYS		.33 ± .011 (5)	.31 ± .014 (5)		.37 ± .014 (5)	A	.38 ± .013 (5)	A	.38 ± .022 (5)	A
LIVER		1.36 ± .059 (5)	1.41 ± .059 (5)		1.84 ± .111 (5)	* A	1.57 ± .048 (5)		1.62 ± .132 (5)	
SPLEEN		.11 ± .009 (5)	.09 ± .007 (5)	B	.12 ± .019 (5)		.12 ± .017 (5)		.14 ± .011 (5)	B
BRAIN/BYWT	*	18.41 ± .478 (5)	19.98 ± .305 (5)	*	16.09 ± .250 (5)	*	18.41 ± .464 (5)		19.78 ± 1.41 (5)	
HEART/BYWT		5.24 ± .176 (5)	5.07 ± .220 (5)		4.21 ± .159 (5)	*	4.93 ± .300 (5)		4.77 ± .145 (5)	
KIDNEYS/BYWT		12.50 ± .509 (5)	12.96 ± .565 (5)		11.56 ± .431 (5)		13.52 ± .668 (5)		14.50 ± .657 (5)	
LIVER/BYWT		51.84 ± 1.81 (5)	58.74 ± 1.25 (5)		57.74 ± 1.85 (5)		56.02 ± 1.22 (5)		61.25 ± 3.23 (5)	
SPLEEN/BYWT		4.27 ± .301 (5)	3.65 ± .168 (5)		3.79 ± .474 (5)		4.14 ± .477 (5)		5.26 ± .343 (5)	
HEART/BRAIN		.29 ± .016 (5)	.25 ± .011 (5)	A	.26 ± .008 (5)		.27 ± .017 (5)		.24 ± .012 (5)	A
KIDNEYS/BRAIN		.68 ± .038 (5)	.65 ± .026 (5)		.72 ± .020 (5)		.73 ± .025 (5)		.74 ± .036 (5)	
LIVER/BRAIN		2.83 ± .149 (5)	2.94 ± .072 (5)		3.60 ± .151 (5)	* A	3.05 ± .060 (5)		3.14 ± .232 (5)	
SPLEEN/BRAIN		.23 ± .019 (5)	.18 ± .010 (5)	B	.24 ± .032 (5)		.23 ± .031 (5)		.27 ± .023 (5)	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 145

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE MICE AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
FINAL WT (G)		32.60 ± 1.03 (5)	34.00 ± 1.82 (5)		37.80 ± .583 (5)		30.80 ± 2.80 (5)		32.00 ± 2.04 (4)	
BRAIN		.51 ± .017 (5)	.53 ± .017 (5)		.51 ± .015 (5)		.48 ± .022 (5)		.50 ± .016 (4)	
HEART		.15 ± .005 (5)	.18 ± .007 (5)	A	.21 ± .004 (5)	+ C	.16 ± .008 (5)		.19 ± .011 (4)	* B
KIDNEYS		.57 ± .043 (5)	.51 ± .030 (5)		.62 ± .024 (5)		.49 ± .057 (5)	A	.50 ± .026 (4)	A
LIVER		1.45 ± .091 (5)	1.68 ± .049 (5)		1.77 ± .071 (5)		1.45 ± .123 (5)		1.59 ± .090 (4)	
SPLEEN		.10 ± .011 (5)	.10 ± .010 (5)		.13 ± .022 (5)	B	.10 ± .010 (5)		.13 ± .013 (4)	B
TESTES		.30 ± .024 (5)	.25 ± .022 (5)	A	.25 ± .016 (5)	A	.23 ± .015 (5)	B	.25 ± .031 (4)	A
BRAIN/BYWT		15.82 ± .798 (5)	15.79 ± .767 (5)		13.58 ± .459 (5)		16.13 ± 1.45 (5)		15.73 ± .550 (4)	
HEART/BYWT		4.75 ± .228 (5)	5.47 ± .323 (5)		5.51 ± .090 (5)		5.32 ± .329 (5)		6.02 ± .561 (4)	
KIDNEYS/BYWT		17.44 ± 1.44 (5)	15.13 ± .529 (5)		16.29 ± .600 (5)		15.89 ± .920 (5)		15.66 ± .260 (4)	
LIVER/BYWT		44.48 ± 2.94 (5)	50.07 ± 2.98 (5)		46.72 ± 1.68 (5)		47.21 ± 1.30 (5)		49.97 ± 1.53 (4)	
SPLEEN/BYWT		3.09 ± .376 (5)	3.01 ± .394 (5)		3.40 ± .521 (5)		3.26 ± .213 (5)		4.07 ± .564 (4)	
TESTES/BYWT		9.09 ± .76[illegible] (5)	7.39 ± .738 (5)		6.69 ± .399 (5)		7.69 ± .303 (5)		7.79 ± .686 (4)	
HEART/BRAIN		.30 ± .008 (5)	.35 ± .009 (5)	A	.41 ± .017 (5)	+ C	.33 ± .016 (5)	A	.38 ± .023 (4)	* B
KIDNEYS/BRAIN		1.10 ± .048 (5)	.96 ± .038 (5)		1.20 ± .051 (5)		1.01 ± .095 (5)		1.00 ± .028 (4)	
LIVER/BRAIN		2.82 ± .141 (5)	3.18 ± .146 (5)		3.45 ± .105 (5)		3.00 ± .214 (5)		3.18 ± .087 (4)	
SPLEEN/BRAIN		.19 ± .014 (5)	.19 ± .019 (5)		.25 ± .045 (5)	B	.21 ± .016 (5)		.26 ± .029 (4)	B
TESTES/BRAIN		.58 ± .048 (5)	.46 ± .036 (5)	A	.50 ± .044 (5)	A	.49 ± .032 (5)	A	.50 ± .050 (4)	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 146

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE MICE AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
FINAL WT (G)		24.80 ± 1.77 (5)	30.60 ± .927 (5)	*	31.00 ± 1.14 (5)	*	30.40 ± .400 (5)	*	29.60 ± .872 (5)	
BRAIN		.50 ± .021 (5)	.51 ± .023 (5)		.56 ± .017 (5)	A	.55 ± .011 (5)		.54 ± .010 (5)	
HEART		.12 ± .009 (5)	.16 ± .007 (5)	B	.14 ± .012 (5)	A	.16 ± .019 (5)	B	.14 ± .006 (5)	A
KIDNEYS		.33 ± .022 (5)	.43 ± .039 (5)	B	.43 ± .025 (5)	B	.40 ± .022 (5)	B	.41 ± .016 (5)	B
LIVER		1.22 ± .047 (5)	1.56 ± .103 (5)	* A	1.41 ± .072 (5)		1.28 ± .070 (5)		1.40 ± .031 (5)	
SPLEEN		.07 ± .007 (5)	.13 ± .011 (5)	+ D	.10 ± .008 (5)	D	.11 ± .013 (5)	D	.14 ± .002 (5)	+ D
BRAIN/BYWT		20.51 ± 1.05 (5)	16.72 ± .415 (5)	*	18.02 ± .739 (5)		18.01 ± .517 (5)		18.18 ± .712 (5)	
HEART/BYWT		4.84 ± .396 (5)	5.17 ± .223 (5)		4.56 ± .281 (5)		5.14 ± .597 (5)		4.75 ± .274 (5)	
KIDNEYS/BYWT		13.34 ± .898 (5)	14.12 ± 1.27 (5)		13.93 ± .545 (5)		13.09 ± .785 (5)		13.99 ± .396 (5)	
LIVER/BYWT		49.69 ± 2.31 (5)	50.83 ± 2.19 (5)		45.54 ± .902 (5)		42.24 ± 2.11 (5)		47.48 ± .642 (5)	
SPLEEN/BYWT		2.78 ± .294 (5)	4.17 ± .280 (5)	* A	3.35 ± .169 (5)		3.50 ± .432 (5)		4.88 ± .132 (5)	+ B
HEART/BRAIN		.24 ± .012 (5)	.31 ± .011 (5)	B	.25 ± .019 (5)		.29 ± .031 (5)	B	.26 ± .010 (5)	A
KIDNEYS/BRAIN		.65 ± .039 (5)	.84 ± .065 (5)		.78 ± .038 (5)		.73 ± .039 (5)		.77 ± .036 (5)	
LIVER/BRAIN		2.43 ± .039 (5)	3.04 ± .110 (5)	* A	2.55 ± .149 (5)		2.35 ± .119 (5)		2.62 ± .089 (5)	
SPLEEN/BRAIN		.13 ± .010 (5)	.25 ± .020 (5)	+ D	.19 ± .014 (5)	C	.19 ± .023 (5)	C	.27 ± .009 (5)	+ D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 147

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE MICE AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP		TREATMENT GROUPS .001 % IN DIET		T R	.005 % IN DIET		T R	.025 % IN DIET		T R	.125 % IN DIET		T R
FINAL WT (G)		32.60 ± 2.54	(5)	30.00 ± 3.34	(4)		30.25 ± 2.29	(4)		40.75 ± 1.93	(4)		36.20 ± 1.46	(5)	
BRAIN		.53 ± .016	(5)	.49 ± .033	(4)		.48 ± .019	(4)		.54 ± .007	(4)		.52 ± .028	(5)	
HEART		.18 ± .007	(5)	.16 ± .027	(4)		.16 ± .014	(4)	A	.18 ± .009	(4)		.17 ± .012	(5)	
KIDNEYS		.53 ± .043	(5)	.45 ± .030	(4)		.49 ± .046	(4)		.63 ± .044	(4)		.60 ± .059	(5)	
LIVER		1.63 ± .168	(5)	1.44 ± .161	(4)		1.85 ± .198	(4)		2.16 ± .124	(4)		2.01 ± .142	(5)	
SPLEEN		.11 ± .015	(5)	.11 ± .013	(4)		.12 ± .015	(4)	A	.15 ± .015	(4)	B	.13 ± .009	(5)	A
TESTES		.26 ± .023	(5)	.21 ± .023	(4)	A	.22 ± .016	(4)	A	.24 ± .009	(4)		.25 ± .016	(5)	
BRAIN/BYWT	*	16.69 ± 1.56	(5)	15.59 ± .707	(4)		15.93 ± .982	(4)		13.26 ± .465	(4)		14.24 ± .334	(5)	
HEART/BYWT		5.48 ± .294	(5)	5.30 ± .294	(4)		5.16 ± .158	(4)		4.54 ± .173	(4)		4.55 ± .259	(5)	
KIDNEYS/BYWT		16.27 ± .601	(5)	14.75 ± .922	(4)		16.14 ± .635	(4)		15.47 ± .627	(4)		16.32 ± .963	(5)	
LIVER/BYWT		49.88 ± 1.99	(5)	47.85 ± 2.30	(4)		60.71 ± 3.33	(4)		53.24 ± 3.19	(4)		55.46 ± 2.14	(5)	
SPLEEN/BYWT		3.41 ± .374	(5)	3.77 ± .339	(4)		4.02 ± .225	(4)		3.59 ± .287	(4)		3.47 ± .159	(5)	
TESTES/BYWT		7.99 ± .485	(5)	7.13 ± .412	(4)		7.36 ± .344	(4)		5.92 ± .371	(4)	* A	6.94 ± .271	(5)	
HEART/BRAIN		.33 ± .017	(5)	.32 ± .031	(4)		.33 ± .024	(4)		.34 ± .013	(4)		.32 ± .022	(5)	
KIDNEYS/BRAIN		1.00 ± .070	(5)	.90 ± .097	(4)		1.03 ± .088	(4)		1.17 ± .065	(4)		1.15 ± .072	(5)	
LIVER/BRAIN		3.11 ± .348	(5)	2.90 ± .183	(4)		3.88 ± .377	(4)		4.01 ± .196	(4)		3.91 ± .201	(5)	
SPLEEN/BRAIN		.21 ± .031	(5)	.23 ± .020	(4)		.26 ± .025	(4)	B	.27 ± .027	(4)	B	.24 ± .010	(5)	A
TESTES/BRAIN		.49 ± .039	(5)	.43 ± .026	(4)	A	.47 ± .026	(4)		.45 ± .021	(4)		.49 ± .015	(5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 148

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE MICE AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
FINAL WT (G)		30.60 ± .927 (5)	28.80 ± 1.46 (5)		32.20 ± 1.28 (5)		29.40 ± .748 (5)		30.00 ± 1.95 (5)	
BRAIN		.53 ± .011 (5)	.53 ± .020 (5)		.55 ± .025 (5)		.56 ± .019 (5)		.58 ± .014 (5)	
HEART		.14 ± .006 (5)	.15 ± .013 (5)		.14 ± .007 (5)		.16 ± .009 (5)		.15 ± .012 (5)	
KIDNEYS		.41 ± .031 (5)	.36 ± .020 (5)	A	.44 ± .022 (5)		.44 ± .017 (5)		.46 ± .039 (5)	A
LIVER		1.36 ± .062 (5)	1.28 ± .072 (5)		1.88 ± .115 (5)	* A	1.55 ± .044 (5)		1.75 ± .154 (5)	
SPLEEN		.10 ± .009 (5)	.09 ± .007 (5)	A	.13 ± .012 (5)	C	.12 ± .015 (5)	B	.14 ± .010 (5)	C
BRAIN/BYWT		17.39 ± .539 (5)	18.54 ± 1.02 (5)		17.18 ± .927 (5)		18.98 ± .738 (5)		19.56 ± 1.21 (5)	
HEART/BYWT		4.75 ± .249 (5)	5.11 ± .500 (5)		4.49 ± .350 (5)		5.34 ± .327 (5)		5.10 ± .322 (5)	
KIDNEYS/BYWT		13.53 ± 1.29 (5)	12.46 ± .602 (5)		13.89 ± .864 (5)		15.07 ± .700 (5)		15.39 ± 1.02 (5)	
LIVER/BYWT	*	44.60 ± 2.07 (5)	44.57 ± 1.05 (5)		58.85 ± 4.47 (5)	*	52.61 ± .668 (5)	*	58.02 ± 2.01 (5)	*
SPLEEN/BYWT		3.26 ± .346 (5)	3.04 ± .171 (5)		4.25 ± .494 (5)		4.16 ± .527 (5)		4.79 ± .397 (5)	
HEART/BRAIN		.27 ± .014 (5)	.27 ± .014 (5)		.26 ± .019 (5)		.28 ± .009 (5)		.26 ± .016 (5)	
KIDNEYS/BRAIN	*	.78 ± .064 (5)	.67 ± .026 (5)		.81 ± .022 (5)		.79 ± .017 (5)		.80 ± .062 (5)	
LIVER/BRAIN		2.58 ± .147 (5)	2.43 ± .130 (5)		3.41 ± .109 (5)	* A	2.79 ± .108 (5)		3.01 ± .220 (5)	
SPLEEN/BRAIN		.19 ± .018 (5)	.17 ± .014 (5)	A	.24 ± .021 (5)	B	.22 ± .024 (5)	A	.25 ± .018 (5)	B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 149

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE MICE AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

			TREATMENT GROUPS							
DEPENDENT VARIABLE	B C	CONTROL GROUP	.001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
FINAL WT (G)		36.60 ± .980 (5)	37.40 ± 1.44 (5)		34.25 ± 1.38 (4)		35.25 ± .750 (4)		38.40 ± .980 (5)	
BRAIN		.55 ± .007 (5)	.51 ± .013 (5)		.51 ± .012 (4)		.52 ± .023 (4)		.51 ± .013 (5)	
HEART		.20 ± .016 (5)	.20 ± .017 (5)		.19 ± .014 (4)		.21 ± .016 (4)		.21 ± .006 (5)	
KIDNEYS		.51 ± .026 (5)	.55 ± .035 (5)		.56 ± .041 (4)	A	.56 ± .032 (4)		.67 ± .031 (5)	* B
LIVER		1.60 ± .041 (5)	1.71 ± .125 (5)		1.58 ± .107 (4)		1.80 ± .106 (4)		2.18 ± .057 (5)	+ A
SPLEEN		.11 ± .011 (5)	.13 ± .025 (5)	A	.12 ± .022 (4)		.11 ± .011 (4)		.16 ± .017 (5)	C
TESTES		.28 ± .012 (5)	.28 ± .023 (5)		.23 ± .010 (4)	A	.25 ± .016 (4)		.27 ± .019 (5)	
BRAIN/BYWT		15.10 ± .378 (5)	13.60 ± .600 (5)		14.94 ± .600 (4)		14.89 ± .843 (4)		13.30 ± .506 (5)	
HEART/BYWT		5.34 ± .383 (5)	5.35 ± .424 (5)		5.62 ± .249 (4)		5.97 ± .549 (4)		5.44 ± .160 (5)	
KIDNEYS/BYWT		13.87 ± .580 (5)	14.74 ± 1.06 (5)		16.40 ± .661 (4)		15.92 ± 1.19 (4)		17.37 ± .678 (5)	
LIVER/BYWT		43.81 ± .535 (5)	45.67 ± 2.91 (5)		46.09 ± 1.42 (4)		51.06 ± 2.68 (4)		56.95 ± 2.33 (5)	+ A
SPLEEN/BYWT		2.98 ± .246 (5)	3.49 ± .631 (5)		3.38 ± .526 (4)		3.00 ± .332 (4)		4.08 ± .516 (5)	
TESTES/BYWT		7.60 ± .155 (5)	7.44 ± .645 (5)		6.82 ± .430 (4)		7.21 ± .469 (4)		7.11 ± .389 (5)	
HEART/BRAIN		.35 ± .024 (5)	.39 ± .025 (5)	A	.38 ± .025 (4)		.40 ± .028 (4)	A	.41 ± .009 (5)	A
KIDNEYS/BRAIN		.92 ± .048 (5)	1.08 ± .060 (5)		1.10 ± .070 (4)		1.07 ± .047 (4)		1.31 ± .070 (5)	+ B
LIVER/BRAIN		2.91 ± .062 (5)	3.37 ± .195 (5)		3.11 ± .208 (4)		3.48 ± .322 (4)		4.29 ± .158 (5)	+ B
SPLEEN/BRAIN		.20 ± .020 (5)	.26 ± .047 (5)	B	.23 ± .043 (4)	A	.20 ± .024 (4)		.30 ± .030 (5)	D
TESTES/BRAIN		.51 ± .021 (5)	.55 ± .039 (5)		.46 ± .028 (4)		.48 ± .015 (4)		.54 ± .042 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 150

EFFECTS OF TNT ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE MICE AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP		TREATMENT GROUPS .001 % IN DIET		T R	.005 % IN DIET		T R	.025 % IN DIET		T R	.125 % IN DIET		T R
FINAL WT (G)		28.25 ± 2.87	(4)	33.20 ± 1.93	(5)		33.20 ± 1.71	(5)		31.00 ± .837	(5)		31.80 ± 1.07	(5)	
BRAIN		.51 ± .010	(4)	.55 ± .018	(5)		.56 ± .016	(5)		.54 ± .024	(5)		.53 ± .018	(5)	
HEART		.15 ± .023	(4)	.15 ± .005	(5)		.16 ± .009	(5)		.16 ± .015	(5)		.15 ± .010	(5)	
KIDNEYS		.38 ± .043	(4)	.43 ± .026	(5)	A	.48 ± .025	(5)	B	.42 ± .031	(5)		.41 ± .026	(5)	
LIVER		1.16 ± .125	(4)	1.53 ± .087	(5)		1.67 ± .111	(5)	* A	1.39 ± .074	(5)		1.61 ± .065	(5)	
SPLEEN		.08 ± .012	(4)	.12 ± .023	(5)	C	.13 ± .008	(5)	D	.09 ± .007	(5)	A	.15 ± .010	(5)	* D
BRAIN/BYWT		18.53 ± 1.54	(4)	16.63 ± .792	(5)		16.85 ± .520	(5)		17.46 ± .581	(5)		16.71 ± .569	(5)	
HEART/BYWT		5.24 ± .467	(4)	4.69 ± .282	(5)		4.95 ± .086	(5)		5.20 ± .479	(5)		4.87 ± .264	(5)	
KIDNEYS/BYWT		13.50 ± .277	(4)	13.03 ± .426	(5)		14.51 ± .560	(5)		13.57 ± .871	(5)		12.89 ± .749	(5)	
LIVER/BYWT		41.16 ± .943	(4)	47.75 ± 2.04	(5)		50.03 ± .960	(5)	*	[illegible]4.66 ± 1.59	(5)		50.76 ± 1.17	(5)	+ A
SPLEEN/BYWT	*	2.92 ± .471	(4)	3.63 ± .653	(5)		3.89 ± .129	(5)		3.03 ± .177	(5)		4.73 ± .398	(5)	*
HEART/BRAIN	*	.29 ± .039	(4)	.28 ± .007	(5)		.29 ± .010	(5)		.30 ± .022	(5)		.29 ± .016	(5)	
KIDNEYS/BRAIN		.75 ± .071	(4)	.79 ± .048	(5)		.86 ± .036	(5)		.77 ± .027	(5)		.77 ± .047	(5)	
LIVER/BRAIN		2.27 ± .201	(4)	2.89 ± .164	(5)		2.99 ± .159	(5)		2.56 ± .095	(5)		3.05 ± .129	(5)	* A
SPLEEN/BRAIN	*	.16 ± .022	(4)	.22 ± .047	(5)		.23 ± .008	(5)	*	.17 ± .010	(5)		.28 ± .025	(5)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 151

EFFECTS OF TNT ON HEMATOLOGY
OF HALF MICE AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
			TREATMENT GROUPS							
RBC (X 10^6)		8.48 ± .180 (2)	8.41 ± .235 (5)		8.62 ± .497 (5)		8.39 ± .199 (5)		7.30 ± .241 (5)	
HGB (G %)		13.60 ± .400 (2)	13.44 ± .325 (5)		14.20 ± .874 (5)		14.12 ± .344 (5)		13.08 ± .453 (5)	
HCT (%)		41.50 ± 1.10 (2)	40.12 ± .835 (5)		42.84 ± 2.47 (5)		41.52 ± 1.16 (5)		37.84 ± 1.26 (5)	
MCV (U)3		47.50 ± .500 (2)	46.60 ± .678 (5)		48.00 ± .447 (5)		48.00 ± .548 (5)		49.80 ± 1.16 (5)	
MCH (UUG)	*	16.10 ± .100 (2)	16.08 ± .208 (5)		16.40 ± .114 (5)		16.80 ± .123 (5)	*	17.90 ± .532 (5)	*
MCHC (%)		33.15 ± .050 (2)	33.94 ± .326 (5)		33.32 ± .394 (5)		34.34 ± .221 (5)		35.08 ± .516 (5)	
WBC (X 10^3)		4.10 ± 1.10 (2)	5.16 ± 757 (5)		6.00 ± .566 (5)		10.04 ± 2.05 (5)		4.36 ± .788 (5)	
PMN (%)	*	12.00 ± 0.00 (2)	13.60 ± 1.63 (5)		11.20 ± 1.16 (5)		11.40 ± 1.03 (5)		21.40 ± 4.70 (5)	
BANDS (%)		0.00 ± 0.00 (3)	1.60 ± .400 (5)	•	1.40 ± .678 (5)	•	2.00 ± .447 (5)	•	1.40 ± .510 (5)	
LYMPH (%)	*	85.00 ± 3.00 (3)	83.40 ± 1.17 (5)		84.60 ± 1.50 (5)		82.80 ± 1.32 (5)		76.20 ± 4.90 (5)	
MONO (%)		.33 ± .333 (3)	.60 ± .600 (5)	•	.60 ± .400 (5)	•	1.40 ± .510 (5)	•	0.00 ± 0.00 (5)	•
EOSIN (%)		0.00 ± 0.00 (3)	.80 ± .583 (5)	•	2.20 ± .663 (5)	•	2.40 ± .927 (5)	•	1.00 ± .548 (5)	•
BASO (%)		0.00 ± 0.00 (3)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 152

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE MICE AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP		TREATMENT GROUPS .001 % IN DIET		T R	.005 % IN DIET		T R	.025 % IN DIET		T R	.125 % IN DIET		T R
RBC (X 10^6)		9.47 ± .475	(3)	7.99 ± .135	(4)		8.18 ± .565	(5)		7.86 ± .240	(5)		7.27 ± .360	(5)	
HGB (G %)		15.47 ± .696	(3)	13.45 ± .419	(4)		14.52 ± .467	(5)		13.24 ± .431	(5)		13.00 ± .555	(5)	
HCT (%)		47.67 ± 2.38	(3)	40.65 ± 1.58	(4)		45.20 ± 2.06	(5)		40.24 ± 1.26	(5)		38.00 ± 1.67	(5)	*
MCV $(U)^3$		48.33 ± .667	(3)	47.25 ± 1.31	(4)		49.20 ± .860	(5)		48.20 ± 1.46	(5)		50.80 ± .583	(5)	
MCH (UUG)		16.43 ± .120	(3)	16.90 ± .430	(4)		16.48 ± .174	(5)		16.90 ± .545	(5)		17.88 ± .373	(5)	
MCHC (%)		33.20 ± .100	(3)	34.17 ± .229	(4)		32.64 ± .578	(5)		33.64 ± .485	(5)		34.52 ± .296	(5)	
WBC (X 10^3)		4.53 ± .581	(3)	2.40 ± .216	(4)		4.92 ± 1.30	(5)		3.64 ± .574	(5)		3.56 ± .624	(5)	
PMN (%)		11.00 ± 6.66	(3)	14.50 ± 3.95	(4)		9.20 ± 1.59	(5)		17.00 ± 3.86	(5)		21.80 ± 3.54	(5)	
BANDS (%)		2.00 ± 1.15	(3)	1.50 ± 1.50	(4)	•	1.40 ± .676	(5)	•	.80 ± .583	(5)	•	.60 ± .245	(5)	•
LYMPH (%)		87.00 ± 5.86	(3)	83.75 ± 3.28	(4)		87.40 ± 1.60	(5)		77.60 ± 5.29	(5)		72.80 ± 4.03	(5)	
MONO (%)	*	0.00 ± 0.00	(3)	.25 ± .250	(4)	•	.20 ± .200	(5)	•	1.00 ± .447	(5)	•	1.40 ± .872	(5)	
EOSIN (%)		0.00 ± 0.00	(3)	0.00 ± 0.00	(4)	•	1.80 ± .916	(5)	•	3.60 ± 1.12	(5)	•	3.40 ± 1.17	(5)	
BASO (%)		0.00 ± 0.00	(3)	0.00 ± 0.00	(4)		0.00 ± 0.00	(5)		0.00 ± 0.00	(5)		0.00 ± 0.00	(5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 153

EFFECTS OF TNT ON HEMATOLOGY
OF MALE MICE AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
RBC (X 10^6)		9.79 ± .180 (5)	9.32 ± .316 (5)		9.68 ± .153 (5)		9.21 ± .506 (4)		8.52 ± .431 (4)	
HGB (G %)	+	16.48 ± .196 (5)	15.36 ± .549 (5)		16.00 ± .141 (5)		13.18 ± 2.02 (4)		15.23 ± .834 (4)	
HCT (%)	+	47.56 ± .549 (5)	44.92 ± 1.08 (5)		46.56 ± .366 (5)		41.75 ± 7.13 (4)		42.03 ± 2.14 (4)	
MCV (U)3		47.00 ± .548 (5)	46.20 ± .583 (5)		46.20 ± .374 (5)		46.50 ± .866 (4)		47.50 ± 1.32 (4)	
MCH (UUG)		16.76 ± .202 (5)	16.40 ± .179 (5)		16.46 ± .103 (5)		16.45 ± .514 (4)		17.73 ± .239 (4)	
MCHC (%)	*	34.90 ± .313 (5)	34.62 ± .512 (5)		34.66 ± .121 (5)		33.22 ± 1.10 (4)		36.47 ± .717 (4)	
WBC (X 10^3)		7.40 ± .456 (5)	6.60 ± 1.09 (5)		7.12 ± .692 (5)		5.85 ± .512 (4)		7.68 ± 1.83 (4)	
PMN (%)		20.40 ± 3.61 (5)	19.80 ± 5.45 (5)		25.40 ± 3.12 (5)		30.25 ± 6.49 (4)		49.00 ± 12.7 (3)	
BANDS (%)		.60 ± .400 (5)	.60 ± .400 (5)		.20 ± .200 (5)	*	1.50 ± .500 (4)	*	2.00 ± 1.00 (3)	*
LYMPH (%)		76.60 ± 3.85 (5)	78.00 ± 5.29 (5)		74.00 ± 3.42 (5)		68.75 ± 6.88 (4)		48.67 ± 13.6 (3)	A
MONO (%)		.60 ± .245 (5)	1.20 ± .374 (5)		.40 ± .245 (5)		0.00 ± 0.00 (4)		.33 ± .333 (3)	
EOSIN (%)		1.80 ± .490 (5)	.40 ± .245 (5)	* C	0.00 ± 0.00 (5)	+ D	0.00 ± 0.00 (4)	+ D	0.00 ± 0.00 (3)	* D
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (4)		0.00 ± 0.00 (3)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 154

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE MICE AFTER [illegible] WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
RBC (X 10^6)		[illegible].31 ± .490	6.68 ± 1.68 (5)		8.86 ± .394 (5)	*	9.62 ± .492 (4)		9.35 ± .471 (5)	
HGB (G %)		[illegible].76 ± .835 (5)	14.50 ± .420 (4)		14.58 ± .641 (5)		16.12 ± .419 (4)		15.74 ± .718 (5)	
HCT (%)		48.36 ± 2.81 (5)	41.50 ± 1.30 (4)		45.62 ± 1.58 (5)		50.53 ± 4.91 (4)		45.80 ± 2.01 (5)	
MCV (U)3		45.00 ± 1.10 (5)	47.50 ± .500 (4)		47.60 ± .927 (5)		48.25 ± .750 (4)		46.00 ± .548 (5)	
MCH (UUG)		16.22 ± .284 (5)	17.23 ± .111 (4)		16.46 ± .189 (5)		16.98 ± .452 (4)		16.92 ± .229 (5)	
MCHC (%)	*	35.12 ± .459 (5)	35.17 ± .131 (4)		32.72 ± 1.06 (5)		33.53 ± 1.78 (4)		35.26 ± .453 (5)	
WBC (X 10^3)		6.88 ± .942 (5)	3.55 ± .538 (4)		5.82 ± 1.61 (5)		8.07 ± .896 (4)		5.98 ± 1.02 (5)	
PMN (%)		19.20 ± 2.73 (5)	17.80 ± 4.76 (5)		20.00 ± 1.64 (5)		20.75 ± 6.14 (4)		20.00 ± 1.67 (5)	
BANDS (%)		.60 ± .400 (5)	0.00 ± 0.00 (5)	•	1.40 ± .872 (5)	•	1.25 ± .947 (4)	•	2.40 ± 1.36 (5)	•
LYMPH (%)		79.40 ± 2.82 (5)	74.60 ± 2.1[illegible] (5)		80.60 ± 2.62 (5)		78.00 ± 5.51 (4)		77.60 ± 1.75 (5)	
MONO (%)		.40 ± .245 (5)	1.40 ± .400 (5)	•	0.00 ± 0.00 (5)	•	0.00 ± 0.00 (4)	•	0.00 ± 0.00 (5)	•
EOSIN (%)		.40 ± .245 (5)	.20 ± .200 (5)		0.00 ± 0.00 (5)	B	0.00 ± 0.00 (4)	A	0.00 ± 0.00 (5)	B
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (4)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 155

EFFECTS OF TNT ON HEMATOLOGY
OF HALF MICE AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
RBC (X 10^6)	*	8.98 ± .305 (5)	9.24 ± .547 (4)		8.40 ± .228 (4)		8.48 ± .054 (4)		8.83 ± .127 (5)	
HGB (G %)	*	14.60 ± .867 (5)	15.50 ± .480 (4)		13.90 ± .342 (4)		14.85 ± .236 (4)		14.56 ± .117 (5)	
HCT (%)	+	46.76 ± 1.27 (5)	48.35 ± 2.34 (4)		36.30 ± 5.46 (4)		43.25 ± .492 (4)	*	43.00 ± .237 (5)	*
MCV (U)3		48.20 ± .735 (5)	48.00 ± 1.08 (4)		46.75 ± .629 (4)		49.50 ± .645 (4)		47.40 ± .748 (5)	
MCH (UUG)		16.36 ± .412 (5)	16.85 ± .433 (4)		16.67 ± .229 (4)		17.48 ± .330 (4)		16.44 ± .172 (5)	
MCHC (%)	*	32.32 ± 1.09 (5)	33.10 ± .534 (4)		34.53 ± .284 (4)		34.67 ± .225 (4)		34.10 ± .391 (5)	
WBC (X 10^3)		5.36 ± 1.68 (5)	8.65 ± 2.41 (4)		5.60 ± 1.19 (4)		6.60 ± 1.46 (4)		8.52 ± .403 (5)	
PMN (%)		22.00 ± 4.34 (5)	28.75 ± 6.02 (4)		21.50 ± 3.77 (4)		22.75 ± 2.29 (4)		19.40 ± 1.69 (5)	
BANDS (%)		0.00 ± 0.00 (5)	.75 ± .479 (4)	•	0.00 ± 0.00 (4)	•	0.00 ± 0.00 (4)	•	0.00 ± 0.00 (5)	
LYMPH (%)		78.00 ± 4.34 (5)	70.50 ± 6.18 (4)		76.25 ± 3.47 (4)		75.50 ± 2.10 (4)		79.60 ± 1.75 (5)	
MONO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (4)	•	.50 ± .500 (4)	•	1.00 ± 0.00 (4)	•	.80 ± .374 (5)	
EOSIN (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (4)	•	1.75 ± .854 (4)	•	.50 ± .289 (4)	•	.20 ± .200 (5)	
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (4)		0.00 ± 0.00 (4)		0.00 ± 0.00 (4)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R - TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 156

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE MICE AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

			TREATMENT GROUPS							
DEPENDENT VARIABLE	BC	CONTROL GROUP	.001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
RBC (X 10^6)		9.12 ± .261 (5)	9.03 ± .218 (5)		8.22 ± .261 (5)		9.49 ± .318 (5)		8.62 ± .374 (4)	
HGB (G %)		15.40 ± .460 (5)	15.56 ± .483 (5)		14.16 ± .515 (5)		16.04 ± .444 (5)		14.65 ± .538 (4)	
HCT (%)		45.44 ± 1.83 (5)	45.20 ± 1.17 (5)		41.48 ± 1.36 (5)		46.44 ± 1.31 (5)		42.40 ± 1.38 (4)	
MCV (U)^3		47.60 ± .400 (5)	49.00 ± .548 (5)		47.80 ± .583 (5)		47.20 ± .490 (5)		48.25 ± .854 (4)	
MCH (UUG)		16.98 ± .199 (5)	17.24 ± .225 (5)		17.26 ± .279 (5)		16.92 ± .193 (5)		17.00 ± .316 (4)	
MCHC (%)	+	34.86 ± .719 (5)	34.82 ± .227 (5)		34.84 ± .197 (5)		35.00 ± .055 (5)		34.87 ± .111 (4)	
WBC (X 10^3)		5.92 ± 1.09 (5)	5.08 ± 1.56 (5)		5.68 ± .905 (5)		4.88 ± .326 (5)		9.40 ± .535 (4)	
PMN (%)		22.00 ± 2.02 (5)	18.40 ± 3.25 (5)		13.20 ± 2.40 (5)	A	18.60 ± 2.32 (5)		19.75 ± 3.30 (4)	
BANDS (%)		.20 ± .200 (5)	0.00 ± 0.00 (5)	*	0.00 ± 0.00 (5)	*	0.00 ± 0.00 (5)	*	.60 ± .400 (5)	*
LYMPH (%)		76.80 ± 2.42 (5)	81.20 ± 3.20 (5)		86.00 ± 2.74 (5)		80.80 ± 2.33 (5)		81.80 ± 3.71 (5)	
MONO (%)		0.00 ± 0.00 (5)	.40 ± .400 (5)	*	.80 ± .800 (5)	*	.20 ± .200 (5)	*	.60 ± .245 (5)	
EOSIN (%)		1.00 ± .633 (5)	0.00 ± 0.00 (5)	B	0.00 ± 0.00 (5)	B	.40 ± .400 (5)		0.00 ± 0.00 (5)	B
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 157

EFFECTS OF TNT ON HEMATOLOGY
OF MALE MICE AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
RBC (X 10^6)		7.94 ± .438 (5)	8.29 ± .222 (5)		8.15 ± .310 (4)		8.48 ± .325 (4)		7.89 ± .193 (5)	
HGB (G %)		13.92 ± .524 (5)	14.48 ± .301 (5)		13.95 ± .320 (4)		14.80 ± .408 (4)		13.64 ± .264 (5)	
HCT (%)		42.92 ± 1.16 (5)	44.72 ± 1.48 (5)		40.55 ± .981 (4)		42.25 ± .922 (4)		40.12 ± .546 (5)	
MCV (U)^3		53.40 ± 2.06 (5)	52.80 ± 1.46 (5)		48.50 ± 1.66 (4)		48.50 ± .866 (4)		50.00 ± 1.14 (5)	
MCH (UUG)		17.44 ± .412 (5)	17.32 ± .384 (5)		17.08 ± .433 (4)		17.40 ± .255 (4)		17.18 ± .376 (5)	
MCHC (%)		32.46 ± .578 (5)	32.48 ± .579 (5)		34.67 ± .397 (4)		35.40 ± .178 (4)	+	34.18 ± .326 (5)	
WBC (X 10^3)		5.84 ± 1.35 (5)	8.24 ± 1.12 (5)		6.95 ± 2.62 (4)		6.30 ± .493 (4)		6.96 ± 2.00 (5)	
PMN (%)	*	15.00 ± 2.08 (4)	20.40 ± 1.12 (5)		21.50 ± 4.77 (4)		37.25 ± 4.33 (4)	*	24.60 ± 7.12 (5)	
BANDS (%)		0.00 ± 0.00 (4)	0.00 ± 0.00 (5)		0.00 ± 0.00 (4)		0.00 ± 0.00 (4)		0.00 ± 0.00 (5)	
LYMPH (%)	*	84.00 ± 2.35 (4)	78.80 ± 1.07 (5)		76.75 ± 4.99 (4)		61.00 ± 4.56 (4)	*	73.50 ± 7.17 (5)	
MONO (%)		1.00 ± .408 (4)	.80 ± .374 (5)	•	1.25 ± .250 (4)	•	1.75 ± .629 (4)	•	1.60 ± .510 (5)	•
EOSIN (%)		0.00 ± 0.00 (4)	0.00 ± 0.00 (5)	•	.50 ± .289 (4)	•	0.00 ± 0.00 (4)	•	0.00 ± 0.00 (5)	•
BASO (%)		0.00 ± 0.00 (4)	0.00 ± 0.00 (5)		0.00 ± 0.00 (4)		0.00 ± 0.00 (4)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 158

EFFECTS OF TNT ON HEMATOLOGY
OF FEMALE MICE AFTER 13 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .001 % IN DIET	T R	.005 % IN DIET	T R	.025 % IN DIET	T R	.125 % IN DIET	T R
RBC (X 10^6)	+	8.63 ± .075 (4)	8.42 ± .229 (5)		6.91 ± 1.78 (5)		7.22 ± 1.87 (5)		8.66 ± .230 (5)	
HGB (G %)		14.35 ± .263 (4)	14.32 ± .403 (5)		15.25 ± .591 (4)		15.50 ± 1.06 (4)		14.24 ± .366 (5)	
HCT (%)		45.85 ± 1.70 (4)	43.60 ± .901 (5)		43.40 ± 1.09 (4)		44.35 ± 2.92 (4)		41.20 ± 1.08 (5)	
MCV (U)3		50.25 ± 1.44 (4)	50.20 ± 1.11 (5)		48.25 ± 1.49 (4)		46.75 ± 1.18 (4)		46.20 ± .374 (5)	
MCH (UUG)		16.48 ± .296 (4)	16.88 ± .338 (5)		17.70 ± .558 (4)		17.10 ± .408 (4)		16.36 ± .147 (5)	
MCHC (%)	+	31.80 ± 1.53 (4)	33.02 ± .413 (5)		35.63 ± .275 (4)		35.63 ± .218 (4)		35.02 ± .229 (5)	
WBC (X 10^3)		8.50 ± .904 (4)	7.48 ± 1.05 (5)		3.70 ± .723 (4)	B	5.05 ± 1.80 (4)		4.56 ± .634 (5)	
PMN (%)	*	21.00 ± 9.70 (4)	14.00 ± 1.45 (5)	*	17.50 ± 2.72 (4)	*	8.60 ± 2.09 (5)	*	8.20 ± 2.48 (5)	*
BANDS (%)		2.25 ± 2.25 (4)	0.00 ± 0.00 (5)	B	0.00 ± 0.00 (5)	B	0.00 ± 0.00 (5)	B	0.00 ± 0.00 (5)	B
LYMPH (%)	*	78.00 ± 9.39 (4)	84.80 ± 1.36 (5)		82.40 ± 2.42 (5)		88.80 ± 2.48 (5)		90.60 ± 2.75 (5)	
MONO (%)		1.00 ± .707 (4)	1.20 ± .374 (5)	*	1.00 ± .775 (5)	*	.60 ± .245 (5)	*	1.26 ± .583 (5)	*
EOSIN (%)		0.00 ± 0.00 (4)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	
BASO (%)		0.00 ± 0.00 (4)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = *TREATMENT-CONTROL CONTRAST* ; R = *TREATMENT-CONTROL RATIO TEST*
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

Table 139

MICROSCOPIC LESIONS IN MALE MICE AFTER 4 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.001	0.005	0.025	0.125
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Colon					
Parasitism				362	
Lung					
Alveolar collapse	301	323,324,325	344	364	381
Alveolar dilation	301	323,324,325			
Hemorrhage	301,303,305		341		
Pneumonia, bronchial			345		
Respiratory disease - chronic			341,342,343 344,345	365	385
Thyroid					
Hyperplasia				364	

Table 160

MICROSCOPIC LESIONS IN FEMALE MICE AFTER 4 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.001	0.005	0.025	0.125
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Colon					
Parasitism			444		
Eye					
Atrophy		422,425			
Lung					
Alveolar collapse			411		
Hemorrhage			411		
Pneumonia, bronchial			443,444	465	
Respiratory disease - chronic		422,425	442,443,444	462,464,465	
Spleen					
Pigmentation (hemosiderosis)					485

Table 161

MICROSCOPIC LESIONS IN MALE MICE AFTER 13 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.001	0.05	0.025	0.125
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Adrenals					
Lymphocytes - interstitial	318				
Colon					
Parasitism	311,313,314				
Heart					
Fibrosis				371	
Kidney					
Lymphocytes - paravascular	312,313,314			371,372,373	391,395
	315			375	
Lung					
Alveolar collapse				371,372,374	392
				375	
Alveolar dilation				372,374,375	392
Congestion				374	
Hemorrhage				373	392
Respiratory disease - chronic	312,313			371,372,373	391,392,
	314,315			374,375	394,395
Pancreas					
Lymphocytes - parenchymal				372	
Spleen					
Pigmentation (hemosiderosis)					391,392,394

Table 162

MICROSCOPIC LESIONS IN FEMALE MICE AFTER 13 WEEKS OF TNT TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.001	0.005	0.025	0.125
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Adrenal					
Lymphocytes - parenchymal					492
Colon					
Parasitism	411				493
Eye					
Atrophy	415			472,473	
Kidney					
Lymphocytes - paravascular	413,414			471,472	491
				473,474	
Lung					
Alveolar collapse	412,413			473	494,495
	414,415				
Alveolar dilation	414,415			473	495
Respiratory disease - chronic	411,413			471,472,473	491,492
	414,415			474,475	493,495
Spleen					
Pigmentation (hemosiderosis)					491,492,493
					494,495
Uterus					
Ectasia - dilated					493
Hyperplasia					494
Vagina					
Inflammation - acute					491

Table 163

MICROSCOPIC LESIONS IN MALE MICE AFTER 4 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (% in Feed)				
	0	0.001	0.005	0.025	0.125
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Colon					
Parasitism					388,389
Liver					
Parasitism				368	
Lung					
Alveolar collapse	310				400
Alveolar histiocytosis					
Congestion					386
Respiratory disease - chronic	306,310			366,370	

Table 164

MICROSCOPIC LESIONS IN FEMALE MICE AFTER 4 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (% in Feed)				
	0	0.001	0.005	0.025	0.125
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Lung					
Alveolar collapse	407				
Alveolar dilation	407				489
Congestion	410				
Respiratory disease - chronic	407				489
Uterus					
Ectasia (dilated)					488

Table 165

MICROSCOPIC LESIONS IN MALE MICE AFTER 13 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (% in Feed)				
	0	0.001	0.005	0.025	0.125
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Kidney					
Lymphocytes - paravascular	320			377,378 379,380	
Liver					
Necrosis					398,400
Lung					
Congestion	318				
Edema	316				
Hemorrhage	318				
Respiratory disease - chronic	319,320			378,379,380	396,397,398
Spleen					
Pigmentation (hemosiderosis)				379	396,397,398 399

Table 166

MICROSCOPIC LESIONS IN FEMALE MICE AFTER 13 WEEKS OF TNT TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (% in feed)				
	0	0.001	0.005	0.025	0.125
	Group Designation				
	A0	A1	A2	A3	A4
	Animal Number				
Adrenal					
Macrophages, lipid-laden				476	
Lymphocytes - interstitial (Stromal CT Cell Prolif in Caps)				480	
Kidney					
Lymphocytes - paravascular	418				498,499
Liver					
Lymphocytes - paravascular	418				498,499
Lung					
Alveolar collapse				479	
Congestion				477	
Respiratory disease - chronic	416,417,418 419,420			478,479,480	499,500
Lymph node					
Hemorrhage					499
Spleen					
Pigmentation (hemosiderosis)	416,419			476,477, 478,480	496,497,498 499,500
Uterus					
Ectasia (dilated)				480	500
Edema					496
Vagina					
Acute inflammation					500

PART 3 - SUBACUTE ORAL TOXICITY STUDIES ON LAP (PHASE II)

INTRODUCTION

This section describes the results of 90-day subacute oral toxicity studies of LAP in dogs, rats, and mice. These studies were performed (1) to define toxic symptoms associated with repeated oral administration of LAP and the target organs or systems; (2) to established a dose-response relationship where possible; (3) to establish no-effect levels for exposure of the species to LAP; and (4) to determine dose levels to be used in chronic studies.

Projected recovery studies in rats and mice were canceled at the request of USAMBRDL so that enough animals for statistical analysis would remain after 13 weeks of treatment with the high dose. This change in the protocol was put into effect when dogs that had undergone 4 weeks of treatment and 4 weeks of recovery were being killed; all dogs remaining on the LAP study were killed at 13 weeks.

EXPERIMENTAL

Studies in Dogs

Forty AKC-registered beagles, approximately 5 months old, were received from Marshall Laboratory Animals, North Rose, New York. The protocol and procedures used were the same as those for the subacute study of TNT except for the following changes:

(1) The TNT and RDX were mixed in the ratio 1.6 to 1.0 (w/w) with lactose powder so that the dose levels were 0.5, 5.0, and 50.0 mg of LAP per kilogram of body weight.

(2) The 17-week sacrifice was omitted, and all dogs surviving after 13 weeks of treatment were killed then.

(3) Dogs were fed dry Purina Field and Farm Kibble daily during quarantine and the test period.

Stock suspensions of LAP in lactose for dosing dogs were prepared in the following manner. For each dose level, an appropriate weight of LAP was dissolved in 100 ml of acetone, and the solution was added to a quantity of lactose sufficient to provide 250 g of stock material.

After stirring to homogeneity, the acetone wet mixture was dried in shallow bowls and covered with aluminum foil for protection from light under a well-ventilated hood. Doses were weighed and placed in the capsules in the manner described for the TNT study in dogs.

Studies in Rats

Eighty male and 80 female Sprague-Dawley-derived rats were used in this study. The protocols and procedures used in the subacute study of TNT were followed, except for the following changes:

(1) Dose levels of LAP in feed were 0.005, 0.05, and 0.5% by weight.

(2) All 20 males and 20 females per group were treated for 13 weeks and survivors were then killed, with no interim sacrifices.

Stock mixtures of the feed were prepared by mixing 2 to 4% TNT and RDX with 1000-g quantities of ground Purina Laboratory Chow in a U.S. Stoneware ball mill. The TNT was added to the chow first and mixed for 30 minutes with the ceramic balls in place. Then the balls were removed, the appropriate amount of RDX was added, and the mixing recommenced and was continued for at least 30 minutes more. The stock mixture was used to prepare the high-dose level (by admixture with an additional amount of rodent chow in the Hobart mixer) and successively lower dose levels in the manner described for TNT. After preparation, samples of feed at each dose level were extracted with dichloromethane and analyzed for their TNT and RDX content by hplc (see below). Stock mixtures and diets were kept in tightly lidded plastic buckets at 4° until use. Diets were prepared fresh every two weeks.

Studies in Mice

One hundred male and 100 female Swiss-Webster mice were used in this study. The procedures and protocols were the same as those for the TNT study, except that--

(1) Dose levels of LAP in the diet were 0.005, 0.05, 0.25, and 0.50% by weight.

(2) All 20 males and 20 females per group were treated for 13 weeks and survivors were then killed; there were no interim or other sacrifices.

Diets for the mice fed LAP were prepared fresh biweekly in the same manner as the diets for rats (described above).

Stability of the LAP Mixture in Feed

The stability of the LAP mixture in feed was determined by passing dichloromethane extracts of feed samples through a short (about 2-inch-long) Florisil column and eluting with the dichloromethane. Elution of RDX depends highly on the activity of the Florisil used; we found that with commercial Florisil, deactivation with 5% water was required before complete recovery of RDX could be attained. The dichloromethane extracts were dried with a rotary evaporator. The residue was taken up in ethyl acetate and analyzed quantitatively by reverse-phase hplc. More than 95% recovery of both TNT and RDX was achieved after the mixture had been in the diet for 4 weeks.

RESULTS

Studies in Dogs

Observations

Once a day, groups of five male and five female dogs each were administered capsules containing 0, 0.5, 5.0, or 50 mg/kg LAP. Beginning almost immediately, the dogs on the high dose vomited frequently and refused to eat. Several of them convulsed, and one male died in convulsions (grand mal type) after the second dose. At least three other dogs appeared to be near death, and blood samples were taken for terminal hematology evaluations. However, the other dogs on the high dose survived.

Almost all the dogs on the high dose had red urine within hours of administration of the first capsule. On Day 2, four of these dogs were inactive. By the end of Week 1, eight of the nine high dose survivors were inactive. This condition persisted in many of these dogs through the next 3 weeks and was occasionally observed thereafter. Two dogs salivated on Day 2 and on two other occasions over the following 12 days. Diarrhea appeared on Day 4 in three dogs and affected as many as seven in the high-dose group until it subsided 3 weeks later; only one animal had diarrhea thereafter. On Day 5, two dogs were noticeably weak. On Day 7, four dogs had dry mouths; on Day 20, three had white gums.

Neurological signs were first noted on Day 6 of treatment, when one dog was wobbling. Two were stiff-legged on Day 7. By Day 10, body fat had been used up and the dogs were emaciated. By Day 11, the dogs were beginning to exhibit poor balance and coordination. Four dogs were swinging their heads the next day. On Day 14, one dog had petit mal convulsions, which recurred frequently for the next 5 weeks. A common observation, beginning on Day 16, was head-bobbing; this response was seen in the surviving high-dose dogs almost throughout the treatment period. On Day 33 two dogs developed a pacing or

circling motion, and on Day 59 one of the remaining high-dose dogs became hyperactive.

The neurological effects were severe in some cases. Seizures of the grand mal type (30 seconds to 2 minutes in duration) were observed in Dog B3-38,* a female, during Week 4. It survived these episodes and, although still exhibiting difficulties with balance and in controlling its head, it appeared to have improved during Weeks 5 through 7; this improvement was concurrent with its recovery in body weight. Dog B3-40 experienced petit mal seizures beginning during Week 4 and lasting through Week 7, and it had difficulty in maintaining its balance; otherwise, its general condition improved over Weeks 5 through 7. All the other dogs on the 50-mg/kg dose regained their activity and general health, although they still had difficulty in controlling the head, and one or two had poor balance through Week 7. Dog B3-33 became increasingly difficult to handle as the study progressed and had a voracious appetite.

Dog B3-36, a female, died suddenly during the sixth treatment week. Its initial reaction to treatment had been relatively mild throughout, characterized by the colored urine, head-bobbing, and somewhat increased activity. On Day 37, this dog was found semiconscious in its cage; the dog was twitching, and the slightest disturbance seemed to initiate convulsions. Blood samples were taken in anticipation of the animal's impending death. When offered food, it initially had difficulty in biting, but then began eating heartily. Two days later, the dog was lying on its side trembling; when it stood, the animal was disoriented and had difficulty remaining upright. The next day, the dog was lying inactive, and was breathing deeply, but otherwise it showed no signs of extreme difficulty. The cause of this dog's death was not ascertained.

Body Weights

Tables 167 and 168 present the weekly body weights for dogs treated with TNT for up to 13 weeks. Both sexes at the 50-mg/kg/day level lost substantial weight during the first 2 weeks. Some stabilization occurred thereafter, except in one male dog that continued to lose weight rapidly during Week 4. This dog was killed at the 4-week sacrifice. Thereafter, the mean body weights of the two males remaining on treatment improved gradually until they were killed (at 13 weeks).

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* B3 is the group designation for high-dose dogs. Odd numbers are males; even numbers are females.

The females at the 50-mg/kg/day level had a significant depression in body weight ($p < 0.05$; A in the r-test) during Weeks 2 through 4. The weakest females at Week 4 were chosen for sacrifice or for recovery, resulting in a sharp increase in mean body weight during Week 5. The condition of one of the females remaining on treatment continued to deteriorate during Week 6, again bringing the mean for the group down. At Week 7, after this female died, the mean showed a second sharp increase and continued to increase gradually until termination (13 weeks).

Females at the 5.0-mg/kg/day level showed an abrupt decrease in mean body weight at Week 5, but this was due to the smaller size of the animals selected at the start of the study to remain on study for 13 weeks. These dogs lost weight slightly from Weeks 5 to 13, but the loss was not significant and improvement was noted during the last 2 weeks. Because of the small number of dogs in each group, we cannot establish whether this is a treatment-related effect; but one female dog in the TNT study that was administered 2.0 mg/kg/day (slightly less TNT by weight than in the LAP mixture administered here) also lost weight during the first 4 weeks of treatment. Therefore, the possibility remains that the mild depression in body weights of females at the 5.0-mg LAP/kg/day level was due to treatment. No similar effects were observed in any other group.

Tables 169 and 170 give the weekly changes in body weights for the dogs undergoing treatment. The decrease in net weight at the 50-mg/kg/day level noted above was significant for males on Week 2 and for females on Weeks 1 and 2. The significant change that resulted for females during Week 9 is spurious and is associated with the zero variance in the two measurements at the high dose. The r-test was not calculable for most of these data.

Tables 171 and 172 present the weekly body weights of the dogs allowed to recover. Both dogs on the high dose substantially improved their body weight upon removal from treatment (Weeks 5 through 8). Although we cannot generalize from group sizes of one, from the magnitude of the change, we conclude that the deterioration in body weight produced by the high dose of LAP was reversed by discontinuation of the treatment.

Tables 173 and 174 present the weekly changes in body weight of the dogs allowed 4 weeks of recovery from the treatment. The great improvement in body weights of dogs at the 50-mg/kg/day level during Week 5 and continuing improvement in this parameter through Week 8 (termination) was evident.

Food Consumption

Tables 175 and 176 present the daily food intake calculations for dogs treated with LAP. Both males and females at the 50-mg/kg/day level decreased food consumption relative to other groups and controls, particularly during week 2. During that week, females practically stopped eating. Their interest in eating was renewed during Weeks 3 and 4, however. Animals remaining on treatment at this level after Week 4 ate well (except for the female that succumbed to the treatment during Week 6). Food consumption by dogs in other groups and in controls was normal throughout the study. In general, food consumption data corresponded with observed changes in weekly body weights of the dogs.

At the end of the 4-week treatment period, the most severely ill were usually killed or placed in the recovery group. Dogs set aside for recovery after 4 weeks were placed in runs separate from those of dogs continuing on treatment. Food consumption for these dogs was not tabulated separately because in most cases they had been paired in runs with other dogs during the treatment period. Dog B3-39 was an exception in that it was the fifth dog in its group and was housed separately. Its food consumption rate can be studied for signs of recovery. It consumed 104, 60, 9, 0, 400, 366, 400, and 400 g/day during Weeks 1 through 8, respectively. During treatment, Dog B3-39 clearly had no interest in food, but its interest revived immediately on termination of treatment. Thus, the suppression of food intake produced by LAP in this dog was immediately reversed on withdrawal from exposure.

Organ Weights

Tables 177 and 178 present organ weights and weight ratios for the dogs killed after 4 weeks of treatment. In the male that received 50 mg of LAP per kg of body weight daily, the liver weight and weight ratios were high, and its testes weight and weight ratios were low. Despite the very low body weight of the female at that dose level, its spleen weight was the greatest of the four dogs killed and its weight ratios were notably high. Organ-to-body weight ratios and some other organ-to-brain weight ratios were also high for that female, but this probably resulted from its low body weight. The heart-to-brain weight for this female was the lowest of any in this study. No other alterations were detected in these dogs that appeared to be treatment-related.

Tables 179 and 180 present the organ weight data for dogs killed after 13 weeks of treatment and no recovery. In the high-dose male, liver weights and weight ratios were high (significantly for ratios) and the testes weights were low. However, apparently the testes-to-body and testes-to-brain weight ratios were not out of line with

other calculated ratios for male dogs. Spleen weights and weight ratios were also marginally high and probably reflected an effect of the treatment. None of the other values was abnormal.

In the females, liver weights and weight ratios for those that received the 50-mg/kg/day level were significantly different from control values. No other alteration was observed in these or the other treated females. (The brains of females at the 5.0 mg/kg/day level were smaller than those of controls, but there was no obvious dose relationship.)

Organ weight data for the recovery dogs are listed in Tables 181 and 182. No appreciable deviations from the normal values for these parameters in dogs were observed in the treated animals, with the possible exception of the testes and testes-to-body and testes-to-brain weight ratios, which did appear to be low for a male of this size. The control male was unusually small, so a number of the values obtained for these parameters in treated males appeared to be altered by the treatment, but actually were not. This control had an unusually small heart and spleen, and its spleen was found to be rough with dark spots at necropsy.

No noticeable effects were discerned in the data of treated females at this sacrifice.

Hematology

Tables 183 and 184 present the hematology data on dogs before treatment, and Tables 185 through 190 present the data collected during treatment. After 4 weeks, Hgb and Hct were significantly low at the 50-mg/kg/day level in both males and females; RBC, though not cited, was precipitously low; MCHC tended to be low in both sexes ($p < 0.01$ in females); and MCV was elevated appreciably in females and was marginally high in males (Tables 185 and 186). PMN and WBC were high (neither significantly) in males. Reticulocytes were increased in dogs of both sexes at this level, and eosinophils were either low or absent. At the 5.0-mg/kg/day level, significantly low MCHC and high reticulocytes were noted for both males and females, suggesting that these changes were dose-related. At the two low-dose levels, eosinophils in males were significantly low when compared with control values; but when compared with the initial values for these dogs, the difference was not great. Reticulocytes in females at these two levels were significantly high, but the values were not abnormal (Table B-8) and arose from the lower value for controls. Most of these alterations persisted up to termination, with a slight improvement in most of these parameters for the males and more substantial recovery for females after 13 weeks (Tables 189 and 190).

At termination, MCHC for both sexes remained significantly low (also for males at the 5.0-mg/kg/day level) and reticulocytes were still elevated at both higher dose levels. MCV and MCH tended to be high in both sexes, although not significantly so. In males, RBC, Hgb, and Hct remained low. Leukocytosis was still evident in males and was noticeable in females by Week 13. Dogs at the high dose had higher PMN than those in all other groups, including controls, at each test period.

Tables 191 and 192 present the hematology data on the dogs killed after 4 weeks of recovery. The only notable observations were the abnormalities in the control male. Its WBC was unusually high, hemoglobin and hematocrit were low, PMN and reticulocytes were increased, and lymphocytes were decreased compared with other control data. This control dog was unusually small, so some of these changes may reflect that, or the animal could have been ill. The only other unusual observation was that the dog was thin.

Female recovery dogs showed a trend toward lower RBC, Hgb, Hct, and MCV as the dose increased. The levels observed in the female at the 50-mg/kg/day level suggested that the dog may not have recovered fully from the anemia.

Clinical Chemistry

Tables 193 through 202 present the clinical chemistry data on dogs before and after treatment with LAP. Before treatment began, the males at the 5.0-mg/kg/day level (Table 193) had low SGOT and iron relative to other groups and controls, but these values were not outside the normal limits (for example, compare with values for females in Table 194). In females that received 5.0 mg/kg/day of LAP, uric acid and phosphorus were low and CO_2 was high ($p < 0.05$), but these values, too, were not appreciably different from those in other groups this size. Therefore, the initial variations in these values were not toxicologically significant.

After 4 weeks of treatment, males and females (Tables 195 and 196) at the 50-mg/kg/day level had high triglycerides relative to their respective controls and to their values before treatment. Serum cholesterol was unaffected. A tendency was observed toward lower globulin and therefore protein (significant for males), and a slight increase in A/G ratio was apparent for both sexes at this level. Creatinine was significantly low ($p < 0.01$) for both sexes that received 50 mg of LAP/kg daily, and the lower values at the 5.0-mg/kg/day level suggest a dose-related trend (Table C-17; $p < 0.01$). BUN for both sexes was elevated, significantly so for females. Serum Ca^{2+} for females at both the high and low doses were low, but the means were within normal limits. SGPT activity was significantly low for males and females at the 50-mg/kg/day level, although it was not necessarily outside the normal limits for either. (This finding is analogous to what we observed in the TNT studies.)

LDH activity was elevated in dogs of both sexes at the highest two doses, significantly so for females ($p < 0.01$); however, neither of these means was significantly different from the means of controls at other times in this study (see, e.g., LDH for male controls at Week 13, Table 199).

In examining the data on dogs that were given the lower doses, the following alterations are cited as being statistically significant: low SGPT for males and low albumin and low serum Ca^{2+} for females at the 0.5-mg/kg/day level. In each case, there was a high degree of variance in the parameter measured, based on the chi-square test. Because of this and because no linear trend (dose response) to the data existed in any of these cases (Table C-17), we believe that these observations resulted from the variability in control values and not in any obvious way from the treatment.

After 8 weeks of treatment (Tables 197 and 198), triglycerides in the dogs that received 50 mg/kg/day remained high (significantly for males) and SGPT was very low ($p < 0.05$; C in the r-test). None of the other parameters found altered at 4 weeks continued to be significantly different after 8 weeks at this dose level. This may be because the more sickly dogs were either killed or set aside for recovery after 4 weeks. Other observations of the clinical chemistry for those dogs that remained on treatment were: the low glucose for males and the high bilirubin for females at the 50-mg/kg/day level (D in the r-test for bilirubin, but these were singular results not found in the means from determinations on blood sera from this group at any other time); high uric acid in males at the two high doses (values that were not outside normal limits and appeared to be significant because of the somewhat low control values); and high total protein for females at the 0.5- and 5.0-mg/kg/day levels (which resulted from the low control mean at this time and not from the treatment).

After 13 weeks of treatment (Tables 199 and 200), the alteration in triglycerides at the high dose level was no longer significant, although it was still observable in the males; and in females the apparent dose-response suggested by the earlier results was obscured by the high triglyceride determinations for the dogs dosed with 0.5 mg/kg/day. The high values at this level appeared to be an anomalous result (see the much lower mean found for this parameter in these dogs at Week 8). Cholesterol levels were also elevated in these animals, and this was the case at Week 8. No other differences existed between females at this treatment level and controls.

As at 4 and 8 weeks, SGPT activity remained significantly depressed in male dogs at the 50-mg/kg/day level but not in females (for males at the 5.0-mg/kg/day level this mean was within the normal range). LDH activity for males was low ($p < 0.01$) at all treatment levels because of the high control values. Creatinine for the two females at the 50-mg/kg/day level was significantly high--the reverse of the

trend observed after 8 weeks of treatment. Since males failed to show this change, the toxicological significance of this result is unclear and possibly is related to the small group size. The high phosphorus determinations also for these females was the highest mean recorded for this parameter, but the mean was well within normal limits (Table B-8) and the values at other levels exhibited no clear dose response. The electrolyte balance for these females was normal (see other clinical chemistry) and appeared to be high because of the lower values for the other groups of female dogs.

Tables 201 and 202 give the clinical chemistry determinations for dogs allowed a 4-week recovery period after treatment. The values are unremarkable except for the low BUN of the male at the 50.0-mg/kg/day level, which value was also low initially and at Week 4. The tendency to low SGPT values for the females at the 5.0- and 50.0-mg/kg/day levels may reflect incomplete recovery of this parameter in these dogs.

Urinalysis

Urine samples from dogs killed on schedule were analyzed. The color of the urine of dogs treated with LAP at 50 mg/kg/day was invariably amber to dark amber or red. No other parameters measured showed any clear relationship to the treatment. However, the male that had been given 5.0 mg/kg/day and killed after 4 weeks did have some unusual signs, including a 1+ turbidity, notably high RBC (10 to 15), moderately large and small round epithelial cells in several large clumps, and many sperm cells in a packed field. These findings may have resulted from contamination during sampling.

Histopathology

Tables 203 and 204 give the histopathology results on dogs killed at the 4-week sacrifice. The male on the high dose (B3) had distinct testicular atrophy with inactive seminiferous tubes and aspermia of the epididymis, which were attributed to the treatment. No treatment-related effects were found either in the female or the male (B3-37) that died early. At the 5.0-mg/kg/day level, both B2 dogs had hyperplasia of the thyroid follicular cells, and the female also had hemosiderosis of the spleen. These effects were not seen in dogs at the higher dose level nor in B1 dogs at the 0.5-mg/kg/day level at this or later sacrifices and therefore cannot be unequivocally ascribed to the treatment.

As Tables 205 and 206 indicate, dogs killed after 13 weeks of treatment showed only one clear effect of treatment: inactive seminiferous tubules in B3-33. Interstitial lymphocytes were seen in the lungs of male B3-33 that had received the highest dose and in one female (B2-30) that had received the next highest dose. This effect may be treatment-related, but the low incidence abrogates a definitive statement on this point. Because of their infrequency of occurrence

and lack of any obvious dose relationship, no other findings at these levels or at the lowest (0.5 mg/kg/day) level were attributable to the treatment. Dog B3-36, the female that died on Day 41, had congestion in the kidney, liver, and lungs not seen in other dogs at this or other sacrifices. These effects may have been related to the mode of death of the animal and not to the treatment.

Tables 207 and 208 present the histopathology results on the dogs that were killed after a 4-week recovery period. The male (B3-39) had testicular atrophy, which signified incomplete recovery of this organ by the time of sacrifice. The granuloma in the lymph node of male B2-27 was not seen in any other dogs in the study. The other findings noted in these tables formed no clear relationship to the treatment. The female (B3-38) had fibrosis and hyperplasia of the thymus and lymphocytes in its cholecyst. No conclusions can be drawn from this.

Studies in Rats

Observations

Rats were treated daily with LAP at 0.005, 0.05, and 0.50% (w/w) in the diet for 13 weeks. Slightly red urine appeared on Day 3 from rats in the 0.05% treatment group, and the intensity of the color increased appreciably by Day 5; this condition persisted throughout the study. In the 0.50% treatment group, red urine was observed earlier (on Day 2), and the color had intensified to bright red by Day 6. Animals in the highest dose group had rough fur, were aggressive, and were notably smaller than the others. No toxic signs were noted in any other groups. During Week 6, the number of deaths increased sharply in the highest treatment group, and this continued through Week 10. More males than females died (see Tables 209 and 210).

Body Weights

Tables 209 and 210 present the weekly body weights of rats for the 13-week treatment period. Rats at the 0.50% LAP level had significantly lower body weights from the first week of treatment through the 13 weeks. The confidence intervals ranged from 20 to 50% lower than the control means over this period. At the end of 4, 8, and 13 weeks, the mean weights for males at this level were 46, 44, and 43% lower than male control means, respectively. The mean weights of females at this level were 39, 37, and 34% lower than the means for the female controls at 4, 8, and 13 weeks, respectively. These data suggest a more pronounced effect of treatment on body weights of males than on females and little, if any, improvement in this parameter with time.

Effects on body weights of rats were seen at the 0.05% LAP level also. The body weights of males were significantly lower than those of their controls during the second week and their growth lagged behind for most of the 13 weeks. The body weights of females were significantly

lower than those of controls on 11 of the 13 treatment weeks. At this treatment level, the female rats apparently were more affected by the treatment than the males--the opposite of the observation made with rats at the 0.50% LAP level compared with their controls. Thus, we cannot determine from body weight data alone whether LAP exerts a preferential effect on the body weights of one sex.

Tables 211 and 212 present the body weight differences for male and female rats during the 13 weeks of treatment. During the first week, both males and females at the high dose lost considerable weight compared with the rats in other treatment groups and with the controls. These animals began to grow during the second week, but their growth rate was more than 50% lower than those of the other groups. The difference in growth rates between high-dose rats and control rats did not disappear until Week 5, but even after that time several instances occurred in which weekly body weights for these groups were still significantly lower than those for controls (note the exception for treated females at Week 8). The reader should consider, however, as pointed out earlier, that a more relevant comparison might be between the growth rates for rats at the 0.50% LAP level and for control rats with the same mean body weights at the start of the week. When compared on that basis, the body weight gain at this level is seen to lag well behind that of controls throughout the treatment period.

An initial retardation in body weight gain followed by accelerated growth during Week 2 was apparent, too, for both males and females at the 0.05% LAP level. Although some changes later in the study were noted as statistically significant at this level, they formed no pattern suggesting that the treatment continued to have an effect on growth rates thereafter.

At the 0.005% LAP level, occasional differences in growth rates of treated and untreated (control) rats occurred, but they did not follow a close relationship to changes at the higher dose levels nor any other consistent pattern that could be related to the treatment.

Food Consumption

Tables 213 and 214 present food consumption data for the control and LAP-exposed rats. Relative to controls, the males and females at the highest dose levels had a depressed food intake initially. At the 0.50% LAP level, the depression was most severe; the animals almost refused to eat during Week 1, but showed much more interest during Week 2 and slowly recovered thereafter. Their food intake after 13 weeks was still appreciably below that of controls, but part, if not all, of this improvement reflected the survival of hardier animals administered the high dose.

The rats given 0.05% LAP also notably improved their food consumption rates during Weeks 2 and 3, and intake stabilized thereafter. In the males, food consumption approached that of controls as the study progressed and became indistinguishable from that of controls by Weeks 12 and 13. The body weights of these males were not different from those of controls at sacrifice. Food consumption of females remained low compared with controls throughout the 13 weeks, and their body weights were also depressed (Table 210).

Males administered the 0.005% level of LAP consumed their food at essentially the same rate as controls throughout. Females fed this level had a lower group body weight at the beginning and maintained that differential throughout the study. Their food consumption rate was also correspondingly lower.

Analysis of the food intake data on the basis of mean body weight appears in Tables 215 and 216. At the 0.50% LAP level, significantly lower rates are cited for both sexes, particularly during the first 3 weeks. These changes are not consistently observed at the lower doses. Considering also net gains or losses in body weights for these groups (Tables 211 and 212), both sexes at the 0.05 and 0.50% LAP levels exhibited decreases in food efficiency during the first week of treatment, but only at the 0.50% level thereafter. At the 0.005% LAP level, there were no appreciable differences in either food intake or food utilization in comparison with controls at any time in the study.

Tables 217 and 218 present the doses of LAP consumed by rats in the diet over the 13-week course of treatment.

Organ Weights

Tables 219 and 220 present the organ weight data and weight ratios for the rats at sacrifice. Several alterations were noted in rats that received the 0.50% LAP level. In males, the heart, kidney, and testes weights were significantly low and the spleen weight was significantly high. Organ-to-brain weight ratios for these organs were altered in the same manner (although not significantly so for the testes). Since body weights were also substantially low relative to controls, body weight ratios were not altered for the heart, kidney, and testes. However, body weight ratios for the liver and brain were high, because these organs were diminished proportionally less than body weight compared with controls. Females at the 0.50% LAP level exhibited the same changes, except that the kidney-to-body weight and liver-to-brain weight ratios were also significantly high. Based on the r-test, the changes in spleen weights were the most dramatic and are clearly treatment-related. The lower testes weights are probably also treatment-related (see Histopathology section). Heart, kidneys, and possibly livers may also be affected by the treatment.

At the 0.05 and 0.005% LAP levels, spleen-to-body weights were significantly high in males. However, these ratios were not outside the range of values we have encountered in these and other studies (e.g., the ratios for control male rats in Tables 85 and 89). In addition, spleen-to-brain weight ratios were comparable for these groups. Microscopic lesions were observed in the spleens of rats from these groups, but at the 0.005% level they were no more frequent than in control males. Consequently, no particular significance was attached to the spleen-to-body weight observation. In contrast, females did exhibit a trend toward higher brain-to-body weight ratios beginning at the 0.05% LAP level ($p < 0.05$) that may be related to the treatment. However, the ratio itself was not abnormally high compared with the ratios obtained for control females in other studies (e.g., the TNT study).

In summary, spleens, kidneys, hearts, and possibly livers of rats appear to be organs specifically affected by ingestion of 0.50% LAP in the daily diet, as well as the testes. All other alterations at this and the 0.05% level arose from the lower body weights of the rats in these groups relative to controls.

Hematology

Tables 221 and 222 give the results of hematology determinations on the rats at sacrifice. In both males and females at the 0.50% LAP level, Hgb and Hct were significantly low. RBC was also low and MCV was high, but neither was cited because of the small numbers of survivors in these groups. Nevertheless, anemia was clear. Other ratios affected because of this condition were low MCHC in males and high MCH in females. Some of these alterations also occurred at the 0.05% LAP level and in the same direction, suggesting that the changes at both levels were dose-related. The leukocyte count for females at the 0.50% level tended to be high, but it was not substantially different from control means encountered in other studies; the mean at the 0.05% LAP level for females, although cited as statistically different, was well within the control range of values for this parameter. The only other significant finding was the low PMN and high lymphocyte percentages of females at the 0.05% LAP level. No dose relationship to these changes was apparent, however; they were attributed to normal intergroup variations rather than to the treatment.

Clinical Chemistry

Tables 223 and 224 present the clinical chemistry data for rats killed after 13 weeks of treatment with LAP. The only alteration common to both males and females at the 0.50% LAP level was the significantly high mean for phosphorus. This mean decreased in both sexes in an apparently dose-related manner, and the alteration remaind significant even at the 0.005% level for females.

Despite the apparent dose-related trend in the data, however, we believe these changes may not be entirely, if at all, due to the treatment. None of these means was outside the range of values encountered for phosphorus in other control animals (for example, the control means ranged from 6.18 to 8.20 for males and from 4.60 to 8.03 for females at the different sacrifices in the TNT study, Part 2). Because of this, it is not possible to discern the shape of the dose-response curve at these treatment levels. In addition, we have found no related pathological alteration to explain this trend. Therefore, we are unable to assess the toxicological significance of this data.

Other apparently significant findings at the 0.50% LAP level were low triglycerides in males but not in females and low glucose and iron and high BUN, cholesterol, bilirubin, and percentage of globulin in females but not in males. The trend toward low iron (noted also in males at both the 0.05 and 0.50% levels) and high serum bilirubin in females may have reflected the more pronounced anemia seen in them than in the males (Tables 221 and 222). The rise in cholesterol was very likely related to the treatment. Male rats generally had lower cholesterol levels than females did, and the mean for males at the 0.50% level, although not cited statistically, was unquestionably high. The mean cholesterol for females at the 0.05% LAP level was also significantly high but was not outside the range of values obtained in other studies on females. When considered with the same observation in females at this level, the high BUN in males at the 0.50% level--although not greatly different from values observed in other control groups--may be treatment-related.

At the lower dose levels, occasional alterations appeared compared with controls, but as with phosphorus (discussed above), a relationship to the treatment cannot be established. The very high LDH activities obtained in all the groups very likely resulted from the rats' pulmonary disease. This condition is difficult to control, and other investigators have also encountered it in the Sprague-Dawley rat.

In summary, the increased cholesterol and probably increased bilirubin(in the females) and the decrease in serum iron were related to the LAP treatment. The increased BUN observed in males at the high dose and the increased phosphrous in the high-dose females may also have been treatment-related. No other findings, including the changes in phosphorus noted at the lower dose levels, were attributed to the treatment.

Histopathology

Tables 225 and 226 give the results of histopathological examination of rat tissues after 13 weeks of LAP treatment. Comparison of the frequency of incidence of each finding as a function of increasing dose reveals that many sporadic lesions were encountered, only a few

of which were treatment-related. The testicular lesions at the 0.5% LAP level, based on their frequency compared with other male groups, were definitely treatment-related, as was the uterine hypoplasia in all high-dose females examined. Hemosiderosis of the spleen occurred in a dose-related manner in males and was common at all levels, including controls, in females.* This effect was also undoubtedly related to the treatment. Although the frequency of incidence was approximately the same in the low-dose and control rats, the condition was more marked in rats in the low-dose group. Hence, it appears that LAP was capable of aggravating the hemosiderosis. The incidence of respiratory defects was high among the rats in this study, but none of the defects appeared to be caused directly by the treatment. The thymus of two of the six males and of one of the ten females that survived treatment at the 0.50% LAP level was hyperplastic, which may indicate an effect of LAP on the immune system. This lesion was not seen with rats treated with TNT.

Studies in Mice

Observations

Mice were treated daily with LAP at 0.005, 0.05, 0.25, and 0.50% (w/w) in the diet. On Days 3 and 2 of treatment, respectively, red urine was observed in the groups that received the intermediate and highest dose levels. The intensity ranged from slightly red to moderately red for the intermediate and highest dose groups, respectively; the color intensity increased as the week progressed, as was observed in rat urine during the first week of that subacute study. Mice had hunched backs in all groups except for control females. There was no pattern to this observation.

As in the rat study, a significant number of unscheduled deaths occurred, particularly among the mice in the highest dose (0.50%) groups (see Tables 227 and 228). Deaths peaked during the second week of treatment but did not abate entirely until the sixth week. In the groups administered 0.25% LAP, the deaths were less numerous. Three control males also died prematurely. All were in different cages. One had slightly rough fur and had been fighting; the second died from fighting; and the third was sickly, inactive, had ruffled fur, a hunched back, and weighed 15 g at death.

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* Spleens in the B1 group were prepared on H & E slides and examined to determine whether any treatment-related effects occurred in the organ at this level.

Body Weights

Tables 227 and 228 give the mean body weights determined weekly for mice in this study. Male and female mice that were fed the 0.50% LAP level had significantly lower body weights than controls did throughout the study. The male mice at the 0.25% LAP level also had significantly lower body weights on 12 of the 13 weeks. The females at the 0.25% and 0.05% levels had lower body weights than controls did; the differences were statistically significant at several weighings. At the 0.05% LAP level, males had noticeably lower body weights than controls did, but the differences were not statistically significant. Neither the males nor females that were administered 0.005% LAP had appreciably different mean body weights from their respective controls except for males at Week 3, but this difference was due to weight losses among control males (above) and not to the treatment.

Tables 229 and 230 show the weight differences among the groups of mice during the study. In general, analysis of these data was restricted to the changes that occurred initially, for reasons stated in the TNT study on mice. The data in these tables show that during the first week, mice at the three higher doses lost weight in contrast to those in other groups. Clearly, the treatment affected mice at these three levels. By the second or third week of the study, mice at the 0.05% LAP level had resumed growth at rates comparable to those of the control groups. Notable improvement was also seen in the growth rates of mice at the highest two dose levels by Week 3, but the weight losses incurred during the first week had not been fully recovered.

Food Consumption

Tables 231 and 232 contain the daily food consumption data for the mice. In the mice fed the two high doses, substantial depression of food intake was observed for Week 1, especially at the 0.50% LAP level. Food intake gradually improved thereafter but at a slower rate at the higher level. By Week 6 and continuing throughout almost the full 13 weeks, both male and female mice surviving the 0.50% LAP diet had consumption rates higher than those of any other group. On one occasion, this increased rate was cited statistically (females, Week 7).

Mice at the 0.05 and 0.005% LAP levels tended to eat at the same rate as controls did throughout the studies, except for males at the 0.005% LAP level, whose food intake rate was slightly higher than those of controls and males at the 0.05% LAP level. No dose relationship was obvious, and since these males tended to be heavier than those in other groups, we consider that this was a normal difference between groups of this size rather than being treatment-related.

In Tables 233 and 234, the data are recalculated in terms of g/kg/day. Food intake rates again are noticeably higher in the animals treated with 0.50% LAP in the diet (often significantly so for females). In addition, food intake is consistently higher (though not significantly) for mice at the 0.25% dose level except for males during Week 12. Despite this, mice in these groups did not gain any more weight than controls did during treatment (Tables 229 and 230). Hence, food efficiency in these groups was lower than in controls. At other dose levels, too, occasionally food intake was higher than corresponding control intake, but not with a consistency or to a degree that suggested a clear relationship to the treatment.

Tables 235 and 236 give the weekly dose of LAP consumed by the mice during the treatment period.

Organ Weights

Tables 237 and 238 present the weights of organs and weight ratios for the LAP-treated mice. At the 0.25 and 0.50% LAP levels, the spleen weight and particularly the spleen-to-body weight and spleen-to-brain weight ratios were higher in males and females than in controls. The results of the TNT and other studies have indicated that these increases are most likely related to the treatment. Other weights statistically different from controls were those for brain, heart, and kidney--all were low, but were within normal limits; the organ-to-brain weight ratios for these organs were not significantly different. The weights of these organs were decreased in a manner roughly proportional to the relative depression in body weights of these groups compared with controls. Liver weights did not decrease to quite the same degree as body weights; thus, the liver-to-body weight ratios in three of the four groups at these levels are significantly high. This may derive from a treatment-related response not discernible in the other parameters.

The kidneys of the females fed 0.05% LAP were smaller than those of controls. The recorded mean was not outside the normal limits and no weight ratios involving the kidneys were significantly altered. Nevertheless, it is possible, considering the trends in these parameters with dose, that an effect was manifested in this organ by treatment with LAP at the 0.05% level.

At the 0.005% LAP level, the male heart weight and heart-to-brain weight ratio confidence intervals differed by 10 to 20% from control means. However, no statistically significant changes in the t-test were detected. The citations in the r-test have been attributed to the normal variability with groups of this size. Therefore, we have concluded that the 0.005% LAP treatment did not affect any of the weight parameters measured.

Hematology

Tables 239 and 240 present the hematology data for the LAP-treated mice at sacrifice. At 0.25 and 0.50% LAP levels, RBC, Hgb, and Hct tended to be low (significantly so in some cases); MCV, MCHC, and MCH were not altered appreciably. A slight leukocytosis was seen in some mice fed the 0.50% level, and it was significant in the females. Reticulocytes were significantly high at both 0.25 and 0.50% LAP in a manner that was clearly dose-related. Monocytes and eosinophil differentials were higher in all dose groups. Reticulocytes were also significantly different in females at the 0.005 and 0.05% LAP levels (only in the 0.05% level for the r-test). These means, however, agree with those that we have obtained in other studies. In spite of these significant differences, it appears that the reticulocyte levels at 0.005 and 0.05% LAP are virtually at the control level. Thus, we cannot ascribe any toxicological significance to these changes in the females at the two lower dose levels.

Some of the other parameters cited as being different from controls were also different at the lower dose levels. Female RBC, Hgb, and Hct and male Hct values at the 0.05% LAP level were between those recorded at the 0.25% LAP level and those at either the 0.005% LAP or control levels. Although the values were not abnormal, they may have reflected a slight trace of anemia in the animals at the 0.05% LAP level.

Histopathology

Tables 241 and 242 summarize the microscopic lesions found in male and female mice treated with LAP for 13 weeks. The incidence of hemosiderosis of the spleen at the two high dose levels was extremely high in both sexes and was high at the 0.05% level as well. This unquestionably stemmed from the treatment. Nematode parasites were found in the colons of 50% or more of the males that received the two high doses and in the ileum of a smaller percentage; in females, the occurrence of parasites was restricted to an equal number of controls and mice at the 0.25% LAP level but not at the 0.50% level. Lymphocyte accumulations were noted in parenchymal cells of mice at the 0.25% LAP level but hardly at all at the higher dose, making the relationship of this finding to the treatment also obscure. Various lung lesions were noted in both males and females at every dose level and in controls. The higher incidence of chronic respiratory disease in males at the 0.50% LAP level relative to the lower level and to controls examined was not matched in females at the 0.50% LAP level, which makes an interpretation of the effect as being dose-related somewhat tenuous. In two high-dose females, hyperplasia of the mucosa in the uterine horns was observed. In the light of effects on the uterus of female rats exposed to LAP, this finding, although infrequent, is possibly treatment-related.

In summary, the only clearly treatment-related effect in mice was hemosiderosis of the spleen at the 0.05, 0.25, and 0.50% LAP levels.

DISCUSSION AND CONCLUSIONS

Studies in Dogs

Five male and five female beagles were treated with 0.5, 5.0, or 50 mg/kg/day of LAP for up to 90 days. One of each sex was killed after 4 weeks, and one dog of each sex was killed 4 weeks later after a recovery period.

At the 0.50-mg/kg/day level, no effects of treatment on any of the parameters measured were detected. Gross and microscopic examination of organs and tissues from the treated dogs showed no alterations attributable to the treatment. Thus, 0.50 mg of LAP/kg/day is a "no-effect" level in the dog.

In the dogs that received 5.0 mg/kg/day, most of the alterations observed were marginal, appeared only once, or could not be clearly attributed to the treatment. The body weights of females may have been depressed, but the group was too small to validate this. Significantly low MCHC ratios and reticulocytosis were observed in both sexes almost throughout the treatment period, and these conditions unquestionably were the result of the slight anemia manifested at this treatment level. The low creatinine values after 4 weeks of treatment may be treatment-related, and the low SGPT in males after 13 weeks surely was, because it was pronounced at the high dose.

At the 50-mg/kg/day level of LAP, toxic symptoms were numerous. Two dogs died, the male almost immediately. The severity of the reaction was unexpected, based on the findings from the earlier range-finding study; but perhaps, in retrospect, it is not surprising in light of the variability of the susceptibility of individual dogs to TNT toxicity.[23] The dogs stopped eating, their body weights dropped dramatically, and organ weights also decreased as body reserves were utilized. Neurological symptoms included grand mal and petit mal convulsions, inactivity followed by hyperactivity in some cases, ataxia, hind-leg rigidity, and particularly bobbing and/or swinging of the head. Red urine and diarrhea occurred, the latter suggesting possible dysfunction in the gastrointestinal tract. The dogs had a pronounced normocytic anemia, with reticulocytosis and a slight leukocytosis. Granulocytosis was almost invariably present, and eosinophils were low or absent. Among the clinical chemistry parameters, the most consistent finding was low SGPT; the treatment probably affected the liver, since changes in SGPT usually reflect changes in the liver. An interesting observation that also appeared to be treatment-related was the elevation of triglyceride levels on Week 4, an effect that disappeared by Week 13, and the opposite development for cholesterol, which was normal on Week 4 and high on Week 13.

At sacrifice, the dogs had hepatomegaly and, in half the cases, enlarged spleens. Testicular atrophy was observed in two of the three high dose males killed while on treatment.

The dogs apparently could adapt to the treatment, at least with respect to some parameters. Thus, the anemia observed on Week 4 had so improved by Week 13 that evidence of it in females was absent. This is not surprising, since the anemia produced by TNT in humans at a dose near the threshold-effect level is temporary and reversible.[21] After the second week, generally the dogs' interest in eating increased, and some effects (such as the inactivity and diarrhea) faded with time.

Discontinuation of treatment resulted in immediate and full recovery in food intake and marked improvement in body weight and in hematology and clinical chemistry measures. The recovery in hematological parameters and body weight was not complete 4 weeks after termination of a 4-week continuous exposure to LAP.

The effects of TNT and of LAP on dogs are contrasted in Table 243. LAP produced toxic responses in the dog that were generally similar to, but more severe than, those produced by TNT. Body weight and food consumption were suppressed (for a longer period with LAP), moderate anemia (characterized by low RBC, Hgb, Hct, and MCHC and elevated MCV) resulted, and SGPT was depressed. Liver and spleen were often enlarged, and the testes of some dogs were smaller. Granulocytosis, low creatinine, and other symptoms (neurological, diarrhea, etc.) were seen in the LAP dogs but not in the dogs exposed to TNT. These differences may only be quantitative, because the dogs given LAP received a higher TNT level (32 mg/kg/day) at the high dose than did the dogs receiving the high dose of TNT (20 mg/kg/day). For these reasons, particularly considering the effect on SGPT but not on SGOT (a unique observation, based on the literature), we conclude that the TNT in the LAP has a major and probably dominating effect on the toxicity of the mixture.

However, some of these differences between the two studies, particularly in the clinical chemistry results, cannot be explained readily on that basis alone. For example, triglycerides, but not cholesterol, were initially affected in the dogs administered LAP, whereas the dogs treated with TNT alone showed only an effect on cholesterol throughout. Considering that the dose of TNT administered to the LAP dogs was higher, one would expect correspondingly high cholesterol levels. The same is true for the elevated bilirubin, decreased iron, and lower A/G ratio seen in dogs given TNT; these measures were seldom altered in dogs treated with LAP. Likewise, we found apparent effects on the kidneys and possibly on the adrenals in the TNT study, which we did not detect in the organ weights of dogs on LAP. These differences suggest that all the effects produced in dogs by LAP should not be ascribed solely to the TNT compound.

Studies in Rats

Rats were treated with 0.005, 0.05, and 0.50% LAP in the diet for 13 weeks without interim sacrifices. At the 0.005% level, no toxicological symptoms or alterations occurred that were unequivocally

Table 243

SUMMARY OF EFFECTS OF CONTINUOUS TNT AND LAP INTAKE IN THREE SPECIES

Dependent Variable	Dogs TNT	Dogs LAP	Rats TNT	Rats LAP	Mice TNT	Mice LAP
Body weight	↓	↓	↓	↓	↓	↓
Food consumption	↓	↓	↓	↓	↓[i]	↑[k]
Adaptation	✓[a]	✓[g]	✓[h]	[j]	✓[f]	[j]
Reversibility	✓[b]	✓[b]	✓[b]	[j]	✓[b]	[j]
Anemia	✓	✓	✓	✓	✓	✓
Leukocytosis		✓	✓			✓
Granulocytosis		✓				
Lymphocytosis			✓			
PMN/Lymphocyte					↑	
BUN				↑		
Uric acid or creatinine		↓	↑			
Cholesterol and/or triglycerides	↑	↑	↑	↑		
Bilirubin	↑		↑[c]	↑		
SGPT	↓	↓	↓			
Fe	↓			↓		
A/G	↓					
Heart				↓		
Liver	↑	↑	↑	↑[c]	↑[c]	
Spleen	↑	↑	↑	↑	↑	↑
Kidneys	↑[c]		↓	↓		
Adrenals	↑[c]					
Testes	↓[c,d]	↓	↓	↓[l]		
Hemosiderosis of spleen	✓[e]	✓[c]	✓	✓	✓	✓
Uterine hypoplasia				✓		
Liver lesions	✓					
Neurological signs	✓	✓		✓		
Colored urine	✓	✓	✓	✓	✓	✓
Unscheduled deaths	✓[f]	✓		✓		✓

a = Possible delayed onset of toxicity.
b = Not complete after 13 weeks of treatment and 4 weeks of recovery.
c = Possible effect on.
d = In 2 of 5 males at the high dose level and 1 of 5 controls.
e = In 1 of 5 females at the high dose level.
f = One dog killed early in anticipation of death.
g = On some but not all parameters.
h = Next to highest dose level of females worsened with time.
i = Temporary.
j = Not evaluated.
k = Temporary depression followed at the high dose by excess food intake.
l = Not significantly lower but atrophy confirmed microscopically.

attributable to the treatment. However, we did note an increase in the severity of the hemosiderosis in the spleens of these rats. This observation needs to be confirmed; the one-year interim sacrifice in the chronic rat study with LAP provides a vehicle for doing so. Pending the outcome of such additional studies, we consider the 0.005% level to be a tentative no-effect level.

At the 0.05% LAP level, body weights and food consumption of rats were depressed and anemia, accompanied by low serum Fe and/or increased bilirubin and cholesterol, was observed in females. The incidence of hemosiderosis of the spleen was increased in these rats compared with controls, a condition that undoubtedly stemmed from the hemolytic anemia still detectable. Toxic effects of the treatment were clearly manifest at this level.

At the 0.50% LAP level, the rats exhibited more extensive and severe symptoms. In addition to depression of body weight gain and food intake, the rats had increased spleen and possibly liver weights, with hemosiderosis, testicular atrophy, decreased heart and kidney weights, uterine hypoplasia, and a normocytic anemia and the accompanying alterations in serum bilirubin and iron, elevated cholesterol and BUN, and phosphorus and red urine.

As with the dogs, many similarities were detected between the effects of TNT and LAP on rats. These include depression of body weight gain and food intake and subsequent retardation of growth; effects on spleens, livers, and testes; anemia; and alterations in cholesterol levels (Table 243).

However, several differences were apparent. Leukocytosis was frequently observed in the rats given the high dose of TNT but not in those given LAP. The PMN and lymphocyte fractions in the leukocytes were altered after 13 weeks; these effects were not seen in rats in the LAP study. Uric acid was high in both studies after 13 weeks, but not significantly so in the LAP study, whereas hypoplasia of the uterus was observed in the LAP but not in the TNT study. In the latter study, SGPT was strongly depressed after 13 weeks of treatment, but no significant depression was observed with LAP. However, in the LAP study, many rats given the high dose had already died, so the rats surviving the treatment may not have been as vulnerable to the effects of TNT in the mixture. Nevertheless, these differences do suggest that in the rat as well as in the dog, TNT is not the sole cause of the toxicity of the LAP mixture.

One difference in results between the TNT and LAP studies is especially noteworthy. With LAP, many unscheduled deaths (by 1 to 6 weeks) occurred in the rats at the 0.50% treatment level. This LAP level contains 0.32% TNT, only slightly higher than the 0.25% used for the high dose in the TNT study. Males and females at the 0.50% LAP level were depleted on the order of 50% or more before the eleventh week;

no more deaths occurred thereafter. This indicates that a cumulative effect of LAP or a metabolite was responsible for these deaths. Since the same effect is observed in mice at the 0.50% LAP level, for which the LD50 is much higher, the effect is less likely to be directly due to unmetabolized components. Animals surviving the treatment probably either were less responsive or were able to eliminate the toxin at a faster rate than those that succumbed.

The causes of these effects were of interest, and we conducted some limited studies to clarify them. To determine the cause of the anemia commonly observed from treatment, we conducted erythrocyte fragility tests to ascertain whether TNT (or a metabolite) was causing hemolysis of the cells. The results of these experiments were negative, suggesting that the anemia did not arise from some direct action of TNT on the red cell wall.[22]

Studies in Mice

Mice were treated at the same dose levels as rats except that an additional treatment group was given 0.25% LAP. At the lowest (0.005%) level, no parameters measured were affected by the treatment. Consequently, we regard this as a "no-effect" level in this study.

At the 0.05% LAP level, both sexes had lower body weights (which did not result from low food intake), a trace of anemia, hemosiderosis of the spleen, and red urine.

At the two highest LAP levels, the effects were similar. Body weight and food intake were both suppressed. However, the mice ate more as the study progressed. Spleens were enlarged, with hemosiderosis evident, and a mild anemia, coupled with pronounced reticulocytosis and mild leukocytosis, was a correlative.

Mortality in mice was much higher at the 0.50% LAP level (40 to 50% mortality during the 13 weeks) than at the 0.25% dose level (5 to 15% mortality). Again, a cumulative effect of the LAP treatment was suggested, but death generally occurred sooner in mice than in rats at the same dose level. Of the many possible explanations for this difference, the most intriguing is that a common TNT metabolite is responsible and that it is produced and accumulates faster in mice than in rats.

Table 243 presents the comparative effects of the TNT and LAP treatments in mice. In most respects, there are no notable differences. One difference, however, is that in contrast to TNT-treated mice, mice treated with LAP at the highest dose level not only overcame an initial aversion to the diet but within a few weeks were eating more than were mice in any other group. This again may be quantitatively related to the dose in that the LAP high dose contained 0.32% TNT by weight, or

about 2.5 times higher than the TNT high dose. This difference in TNT content at the high dose could also explain the leukocytosis in LAP-treated mice, but not the change in PMN-to-lymphocyte ratio in those treated with TNT. Table 244 summarizes the no-effect levels found for both TNT and LAP in the three species tested.

Table 244

"NO OBSERVABLE EFFECTS" LEVELS IN SUBACUTE TOXICITY STUDIES

	TNT		LAP	
Animal	mg/kg/day	% (w/w) in Diet	mg/kg/day	% (w/w) in Diet
Dog	0.20		0.50	
Rat	--	0.002	--	0.005*
Mouse	--	0.005	--	0.005

* Tentative.

Two-Year Chronic Studies

On the basis of this work, the dose levels tentatively recommended for the 2-year chronic study in rats or mice are 0.0032, 0.032, and 0.32% LAP in the diet. These levels contain the same amount of TNT as proposed for the TNT study and therefore would allow some inferences to be made about whether TNT is responsible for any tumors observed in the LAP study. The high-dose LAP level in rats would be the highest tolerable, and therefore the most likely to permit detection and quantitation of tumors. This dose is not close enough to the 0.50% LAP level to result in too many deaths from the treatment during the long-term study. This conclusion is derived from the mortality in the mouse study and from the steepness of the response in rats to dose in the acute oral LD50. We think that this selection of dose levels is satisfactory, based also on the low mortality (5%) in the 28-day rat study (Part 4) at the 0.3% LAP level. The 0.0032% LAP level is lower than the 0.005% level at which LAP appears to aggravate hemosiderosis in rat spleens, and therefore is less likely to produce this effect in the chronic study.

Part 3

Water Quality Criteria

As in the case of TNT, data on human exposure and on long-term mammalian toxicity of the LAP mixture for use in establishing water quality criteria do not exist. In the absence of such data, a suggested approach is to extrapolate interim limits from toxicity studies on a representative mixture of the LAP components in water effluents. This alternative is adopted here in order to calculate maximum concentrations for the effluent that can be considered to minimize risks of adverse effects to the human populations.

For purposes of making the calculation, the approach proposed by the Environmental Protection Agency for nonstochastic effects is used.[34] The highest clear "no observable effect levels" for the LAP mixture in the three subacute studies were 0.5, 3.57* and 8.28† mg/kg/day from the dog, rat, and mouse data, respectively. Using the same uncertainty factor of 1000 as was used earlier (Part 2, Discussion and Conclusions), the corresponding ADIs are 0.5, 3.57, and 8.28 μg/kg/day.

The bioconcentration factor (R) for RDX has been experimentally determined. Bentley and co-workers[37] reported a value of 4.7 for bluegill muscle after exposure of the fish to RDX for 28 days. This value is less than half that calculated for TNT. Since the ratio of TNT to RDX in LAP is 1.6:1, R for LAP is (11.5 x 1.6/2.6) + (4.7 x 1/2.6) or 8.9. Using Equation 1 for calculating C as before (Part 2, Discussion and Conclusions), the calculated water concentrations for LAP are 16.2, 115, and 268 μg/liter (ppb) from the dog, rat, and mouse data, respectively. Thus, there is nearly a 17-fold range among the calculated water concentrations, depending on the species used as a reference.

Since LAP(I) contains only 0.32% TNT and 10% RDX, and since the constituents making up the remaining 90% of LAP(I) and their bioconcentration factors are unknown, no water concentration values for LAP(I) can be calculated.

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* From Tables 217 and 218.

† From Tables 253 and 254.

TABLE 167

EFFECTS OF LAP ON BODY WEIGHTS (KG)
OF MALE DOGS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
INITIAL		10.4 ± .867 (5)	10.7 ± .671 (5)		10.9 ± .392 (5)		10.6 ± .726 (5)	
WEEK 1		10.4 ± .762 (5)	10.7 ± .629 (5)		10.9 ± .438 (5)		9.4 ± .517 (4)	
WEEK 2		10.4 ± .829 (5)	10.6 ± .639 (5)		11.1 ± .357 (5)		8.6 ± .587 (4)	
WEEK 3		10.4 ± .763 (5)	10.5 ± .696 (5)		11.1 ± .415 (5)		8.6 ± .417 (4)	
WEEK 4		10.3 ± .768 (5)	10.5 ± .677 (5)		11.1 ± .426 (5)		8.0 ± .165 (4)	
WEEK 5		10.1 ± 1.00 (4)	10.7 ± 1.07 (3)		10.9 ± .376 (3)		8.1 ± .150 (2)	
WEEK 6		10.1 ± 1.00 (4)	10.7 ± .517 (3)		10.9 ± .436 (3)		8.5 ± .200 (2)	
WEEK 7		10.2 ± 1.12 (4)	11.0 ± .817 (3)		10.9 ± .586 (3)		8.9 ± .050 (2)	
WEEK 8		10.2 ± .939 (4)	11.1 ± .950 (3)		10.8 ± .689 (3)		9.1 ± .050 (2)	
WEEK 9		10.9 ± .833 (3)	11.1 ± 1.00 (3)		11.0 ± .681 (3)		9.2 ± 0.00 (2)	
WEEK 10		10.9 ± .784 (3)	11.0 ± .917 (3)		11.0 ± .721 (3)		9.2 ± .200 (2)	
WEEK 11		10.9 ± .784 (3)	11.0 ± .917 (3)		11.0 ± .801 (3)		9.1 ± .150 (2)	
WEEK 12		11.0 ± .736 (3)	11.0 ± .987 (3)		11.1 ± .801 (3)		9.4 ± .050 (2)	
WEEK 13		11.4 ± .689 (3)	11.5 ± .961 (3)		11.6 ± .845 (3)		9.6 ± .250 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 168

EFFECTS OF LAP ON BODY WEIGHTS (KG)
OF FEMALE DOGS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
INITIAL	*	10.1 ± .147 (5)	9.9 ± .805 (5)		9.8 ± .573 (5)		9.9 ± .217 (5)	
WEEK 1		10.0 ± .234 (5)	9.9 ± .797 (5)		10.0 ± .523 (5)		8.3 ± .258 (5)	
WEEK 2		9.8 ± .252 (5)	9.9 ± .835 (5)		10.0 ± .473 (5)		7.3 ± .260 (5)	* A
WEEK 3		9.7 ± .315 (5)	9.9 ± .783 (5)		10.0 ± .523 (5)		7.0 ± .404 (5)	* A
WEEK 4		9.8 ± .325 (5)	9.7 ± .703 (5)		10.2 ± .452 (5)		7.2 ± .594 (5)	* A
WEEK 5		9.9 ± .119 (4)	9.8 ± 1.09 (3)		9.5 ± .513 (3)		8.4 ± .524 (3)	
WEEK 6		9.9 ± .170 (4)	9.9 ± 1.02 (3)		9.5 ± .524 (3)		8.1 ± .557 (3)	
WEEK 7		9.9 ± .275 (4)	9.8 ± 1.00 (3)		9.6 ± .529 (3)		8.9 ± .150 (2)	
WEEK 8		9.9 ± .309 (4)	9.7 ± .968 (3)		9.4 ± .448 (3)		8.9 ± .050 (2)	
WEEK 9		10.0 ± .273 (3)	9.5 ± .954 (3)		9.2 ± .418 (3)		9.3 ± .050 (2)	
WEEK 10		10.2 ± .384 (3)	9.5 ± 1.02 (3)		9.0 ± .338 (3)		9.3 ± 0.00 (2)	
WEEK 11		10.1 ± .441 (3)	9.5 ± .851 (3)		8.9 ± .338 (3)		9.4 ± .050 (2)	
WEEK 12		10.1 ± .361 (3)	9.5 ± .733 (3)		9.0 ± .328 (3)		9.3 ± .150 (2)	
WEEK 13		10.3 ± .265 (3)	10.1 ± .667 (3)		9.2 ± .328 (3)		9.9 ± .050 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 169

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHT (KG)
OF MALE DOGS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.5 MG/KG/DAY	T	R	5.0 MG/KG/DAY	T	R	50 MG/KG/DAY	T	R
			TREATMENT GROUPS								
WEEK 1	+	.0 ± .132 (5)	.0 ± .092 (5)		*	.0 ± .051 (5)		*	-.9 ± .494 (4)		*
WEEK 2		.0 ± .092 (5)	-.2 ± .040 (5)		*	.2 ± .086 (5)		C	-.8 ± .125 (4)	+	
WEEK 3	+	.0 ± .081 (5)	-.1 ± .068 (5)		*	.0 ± .074 (5)		*	-.1 ± .566 (4)		*
WEEK 4	+	-.1 ± .063 (5)	.0 ± .103 (5)		*	0.0 ± .084 (5)		*	-.6 ± .502 (4)		*
WEEK 5		-.1 ± .085 (4)	-.1 ± .285 (3)		*	.3 ± .088 (3)		*	.4 ± .100 (2)		A
WEEK 6		.0 ± .048 (4)	0.0 ± .265 (3)		*	.0 ± .067 (3)		*	.3 ± .050 (2)		*
WEEK 7		.1 ± .160 (4)	.3 ± 0.00 (3)		*	0.0 ± .208 (3)		*	.4 ± .150 (2)		*
WEEK 8	+	0.0 ± .187 (4)	.1 ± .133 (3)		*	-.1 ± .120 (3)		*	.2 ± 0.00 (2)		*
WEEK 9		0.0 ± .058 (3)	0.0 ± .058 (3)		*	.2 ± .033 (3)		*	.1 ± .050 (2)		*
WEEK 10		0.0 ± .058 (3)	-.1 ± .088 (3)		*	0.0 ± .058 (3)		*	0.0 ± .200 (2)		*
WEEK 11		0.0 ± 0.00 (3)	0.0 ± 0.00 (3)		*	.0 ± .088 (3)		*	-.1 ± .050 (2)		*
WEEK12		.1 ± .058 (3)	1 ± .133 (3)		*	.1 ± 0.00 (3)		*	.2 ± .100 (2)		*
WEEK 13		.4 ± .058 (3)	.5 ± .067 (3)			.4 ± .088 (3)			.4 ± .300 (2)		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 170

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHT (KG)
OF FEMALE DOGS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T	R	5.0 MG/KG/DAY	T	R	50 MG/KG/DAY	T	R
WEEK 1		-.1 ± .141 (5)	0.0 ± .123 (5)		•	.1 ± .128 (5)		•	-1.6 ± .097 (5)	+	
WEEK 2		-.3 ± .117 (5)	-.1 ± .068 (5)		•	.1 ± .075 (5)		•	-1.0 ± .103 (5)	+	•
WEEK 3		-.1 ± .068 (5)	.0 ± .133 (5)		•	.0 ± .075 (5)		•	-.3 ± .192 (5)		
WEEK 4	*	.1 ± .051 (5)	-.2 ± .120 (5)		•	.2 ± .153 (5)		•	.2 ± .332 (5)		•
WEEK 5		-.2 ± .132 (4)	-.1 ± .208 (3)		•	-.2 ± .219 (3)		•	.3 ± .088 (3)		
WEEK 6		.0 ± .155 (4)	.0 ± .088 (3)		•	.0 ± .088 (3)		•	-.3 ± .133 (3)		•
WEEK 7	*	.0 ± .225 (4)	-.1 ± .033 (3)		•	.1 ± .033 (3)		•	.2 ± .300 (2)		•
WEEK 8		-.1 ± .095 (4)	-.1 ± .067 (3)		•	-.2 ± .088 (3)			.1 ± .100 (2)		•
WEEK 9		-.1 ± .067 (3)	-.2 ± .033 (3)			-.1 ± .088 (3)			.3 ± 0.00 (2)	*	
WEEK 10		.1 ± .120 (3)	.0 ± .088 (3)		•	-.3 ± .088 (3)		•	.1 ± .050 (2)		•
WEEK 11		.0 ± .120 (3)	.0 ± .167 (3)		•	-.1 ± 0.00 (3)		•	.2 ± .050 (2)		•
WEEK12		.0 ± .088 (3)	.0 ± .120 (3)		•	.2 ± .033 (3)		•	-.2 ± .100 (2)		•
WEEK 13		.2 ± .200 (3)	.5 ± .067 (3)		•	.2 ± .173 (3)			.7 ± .100 (2)		•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 171

EFFECTS OF LAP ON BODY WEIGHTS (KG)
OF MALE DOGS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	5.0 MG/KG/DAY	50 MG/KG/DAY
INITIAL	10.4 (5)	11.5 (1)	10.5 (1)	12.5 (1)
WEEK 1	10.4 (5)	11.3 (1)	10.6 (1)	10.8 (1)
WEEK 2	10.4 (5)	11.3 (1)	10.8 (1)	10.3 (1)
WEEK 3	10.4 (5)	11.4 (1)	10.9 (1)	9.3 (1)
WEEK 4	10.3 (5)	11.1 (1)	11.0 (1)	8.2 (1)
WEEK 5	10.1 (4)	10.9 (1)	11.0 (1)	8.8 (1)
WEEK 6	10.1 (4)	10.5 (1)	10.4 (1)	9.4 (1)
WEEK 7	10.2 (4)	10.6 (1)	10.6 (1)	10.0 (1)
WEEK 8	10.2 (4)	10.5 (1)	10.5 (1)	10.6 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES.   LAP ADMINISTERED DAILY BY CAPSULE.

TABLE 172

EFFECTS OF LAP ON BODY WEIGHTS (KG)
OF FEMALE DOGS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	5.0 MG/KG/DAY	50 MG/KG/DAY
INITIAL	10.1 (5)	10.2 (1)	12.0 (1)	9.1 (1)
WEEK 1	10.0 (5)	10.5 (1)	11.9 (1)	7.4 (1)
WEEK 2	9.8 (5)	10.4 (1)	11.7 (1)	6.6 (1)
WEEK 3	9.7 (5)	10.8 (1)	11.9 (1)	6.3 (1)
WEEK 4	9.8 (5)	10.4 (1)	11.8 (1)	6.4 (1)
WEEK 5	9.9 (4)	10.4 (1)	11.9 (1)	7.4 (1)
WEEK 6	9.9 (4)	10.2 (1)	12.0 (1)	8.0 (1)
WEEK 7	9.9 (4)	10.1 (1)	12.2 (1)	8.8 (1)
WEEK 8	9.9 (4)	10.2 (1)	12.2 (1)	9.1 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE.

TABLE 173

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHT (KG)
OF MALE DOGS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	5.0 MG/KG/DAY	50 MG/KG/DAY
WEEK 1	.0 (5)	-.2 (1)	0.0 (1)	-1.7 (1)
WEEK 2	.0 (5)	0.0 (1)	.2 (1)	-.5 (1)
WEEK 3	.0 (5)	.1 (1)	.1 (1)	-1.0 (1)
WEEK 4	-.1 (5)	-.3 (1)	.1 (1)	-1.1 (1)
WEEK 5	-.1 (4)	-.2 (1)	0.0 (1)	.6 (1)
WEEK 6	.0 (4)	-.4 (1)	-.6 (1)	.6 (1)
WEEK 7	.1 (4)	.1 (1)	.2 (1)	.6 (1)
WEEK 8	0.0 (4)	-.1 (1)	-.1 (1)	.6 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE.

TABLE 174

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHT (KG)
OF FEMALE DOGS DURING 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	5.0 MG/KG/DAY	50 MG/KG/DAY
WEEK 1	-.1 (5)	.3 (1)	-.1 (1)	-1.7 (1)
WEEK 2	-.3 (5)	-.1 (1)	-.2 (1)	-.8 (1)
WEEK 3	-.1 (5)	.4 (1)	.2 (1)	-.3 (1)
WEEK 4	.1 (5)	-.4 (1)	-.1 (1)	.1 (1)
WEEK 5	-.2 (4)	0.0 (1)	.1 (1)	1.0 (1)
WEEK 6	.0 (4)	-.2 (1)	.1 (1)	.6 (1)
WEEK 7	.0 (4)	-.1 (1)	.2 (1)	.8 (1)
WEEK 8	-.1 (4)	.1 (1)	0.0 (1)	.3 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE.

TABLE 175

EFFECTS OF LAP ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE DOGS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLES	CONTROL GROUP	TREATMENT GROUPS 0.5 MG/KG/DAY	5.0 MG/KG/DAY	50.0 MG/KG/DAY
WEEK 1	385.2	400.0	400.0	194.7
WEEK 2	397.6	393.1	400.0	130.9
WEEK 3	398.2	395.5	400.0	145.6
WEEK 4	400.0	398.5	400.0	216.6
WEEK 5	400.0	400.0	400.0	400.0
WEEK 6	400.0	381.7	400.0	383.4
WEEK 7	400.0	372.6	400.0	400.0
WEEK 8	400.0	390.3	400.0	390.2
WEEK 9	400.0	400.0	400.0	400.0
WEEK 10	400.0	400.0	400.0	400.0
WEEK 11	400.0	400.0	400.0	400.0
WEEK 12	400.0	400.0	400.0	400.0
WEEK 13	400.0	400.0	400.0	400.0

ENTRIES ARE MEANS. GROUP N SAME AS IN BODY WEIGHT TABLE.
LAP WAS ADMINISTERED DAILY BY CAPSULE

TABLE 176

EFFECTS OF LAP ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE DOGS DURING 13 WEEKS OF TREATMENT

		TREATMENT GROUPS		
DEPENDENT VARIABLES	CONTROL GROUP	0.5 MG/KG/DAY	5.0 MG/KG/DAY	50.0 MG/KG/DAY
WEEK 1	313.4	370.5	347.8	105.2
WEEK 2	282.8	343.0	357.4	17.8
WEEK 3	306.6	345.4	356.9	124.7
WEEK 4	351.0	353.5	356.2	306.2
WEEK 5	365.3	357.7	341.3	389.2
WEEK 6	360.1	378.5	373.3	260.5
WEEK 7	340.6	352.6	337.2	274.6
WEEK 8	359.9	347.6	345.6	251.9
WEEK 9	360.1	338.0	304.4	353.5
WEEK 10	391.6	375.3	392.3	334.7
WEEK 11	380.4	363.7	392.8	340.3
WEEK 12	361.8	367.4	400.0	291.7
WEEK 13	400.0	367.9	400.0	366.2

ENTRIES ARE MEANS. GROUP N SAME AS IN BODY WEIGHT TABLE.
LAP WAS ADMINISTERED DAILY BY CAPSULE

TABLE 177

EFFECTS OF LAP ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	5.0 MG/KG/DAY	50 MG/KG/DAY
FINAL WEIGHT (KG)	10.60 (1)	8.60 (1)	12.70 (1)	8.20 (1)
BRAIN	81.01 (1)	87.04 (1)	88.00 (1)	79.32 (1)
HEART	91.10 (1)	89.40 (1)	111.70 (1)	97.10 (1)
KIDNEYS	51.44 (1)	49.50 (1)	76.52 (1)	47.32 (1)
LIVER	335.61 (1)	247.50 (1)	443.26 (1)	489.02 (1)
SPLEEN	32.15 (1)	28.62 (1)	43.42 (1)	38.56 (1)
GONADS	19.52 (1)	16.64 (1)	21.56 (1)	8.47 (1)
ADRENAL	2.21 (1)	2.14 (1)	1.96 (1)	1.62 (1)
THYROID	1.07 (1)	2.12 (1)	2.14 (1)	.95 (1)
BRAIN/BODY	7.64 (1)	9.89 (1)	6.93 (1)	9.67 (1)
HEART/BODY	8.59 (1)	10.16 (1)	8.80 (1)	11.84 (1)
KIDNEY/BODY	4.85 (1)	5.63 (1)	6.03 (1)	5.77 (1)
LIVER/BODY	31.66 (1)	28.13 (1)	34.90 (1)	59.64 (1)
SPLEEN/BODY	3.03 (1)	3.25 (1)	3.42 (1)	4.70 (1)
GONADS/BODY	1.84 (1)	1.89 (1)	1.70 (1)	1.03 (1)
ADRENAL/BODY	.21 (1)	.24 (1)	.15 (1)	.20 (1)
THYROID/BODY	.10 (1)	.24 (1)	.17 (1)	.12 (1)
HEART/BRAIN	1.12 (1)	1.03 (1)	1.27 (1)	1.22 (1)
KIDNEY/BRAIN	.64 (1)	.57 (1)	.87 (1)	.60 (1)
LIVER/BRAIN	4.14 (1)	2.84 (1)	5.04 (1)	6.17 (1)
SPLEEN/BRAIN	.40 (1)	.33 (1)	.49 (1)	.49 (1)
GONADS/BRAIN	.24 (1)	.19 (1)	.25 (1)	.11 (1)
ADRENAL/BRAIN	.03 (1)	.02 (1)	.02 (1)	.02 (1)
THYROID/BRAIN	.01 (1)	.02 (1)	.02 (1)	.01 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE.

TABLE 178

EFFECTS OF LAP ON ORGAN WEIGHTS (G), ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G) OF FEMALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	5.0 MG/KG/DAY	50 MG/KG/DAY
FINAL WEIGHT (KG)	8.55 (1)	3.50 (1)	10.00 (1)	5.50 (1)
BRAIN	80.87 (1)	82.14 (1)	86.21 (1)	88.14 (1)
HEART	90.20 (1)	95.00 (1)	79.40 (1)	61.10 (1)
KIDNEYS	42.45 (1)	41.62 (1)	46.22 (1)	49.11 (1)
LIVER	259.80 (1)	271.30 (1)	335.54 (1)	240.41 (1)
SPLEEN	30.76 (1)	26.34 (1)	30.60 (1)	57.33 (1)
GONADS	1.36 (1)	2.73 (1)	2.91 (1)	2.53 (1)
ADRENAL	1.25 (1)	3.04 (1)	2.14 (1)	3.26 (1)
THYROID	.88 (1)	2.76 (1)	1.17 (1)	1.64 (1)
BRAIN/BODY	9.49 (1)	9.66 (1)	8.62 (1)	16.03 (1)
HEART/BODY	9.44 (1)	11.18 (1)	7.94 (1)	11.11 (1)
KIDNEY/BODY	4.99 (1)	4.90 (1)	4.62 (1)	8.93 (1)
LIVER/BODY	30.56 (1)	31.88 (1)	33.55 (1)	43.71 (1)
SPLEEN/BODY	3.62 (1)	3.33 (1)	3.06 (1)	10.42 (1)
GONADS/BODY	.16 (1)	.32 (1)	.29 (1)	.46 (1)
ADRENAL/BODY	.15 (1)	.36 (1)	.21 (1)	.59 (1)
THYROID/BODY	.10 (1)	.32 (1)	.12 (1)	.30 (1)
HEART/BRAIN	.99 (1)	1.16 (1)	.92 (1)	.69 (1)
KIDNEY/BRAIN	.53 (1)	.51 (1)	.54 (1)	.56 (1)
LIVER/BRAIN	3.22 (1)	3.30 (1)	3.89 (1)	2.73 (1)
SPLEEN/BRAIN	.38 (1)	.35 (1)	.35 (1)	.65 (1)
GONADS/BRAIN	.02 (1)	.03 (1)	.03 (1)	.03 (1)
ADRENAL/BRAIN	.02 (1)	.04 (1)	.02 (1)	.04 (1)
THYROID/BRAIN	.01 (1)	.03 (1)	.01 (1)	.02 (1)

ENTRIES ARE MEANS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE.

TABLE 179

EFFECTS OF LAP ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE DOGS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T	R	5.0 MG/KG/DAY	T	R	50 MG/KG/DAY	T	R
FINAL WEIGHT (KG)		11.37 ± .727 (3)	11.30 ± 1.05 (3)			11.23 ± .649 (3)			9.75 ± .250 (2)		
BRAIN		84.20 ± 2.29 (3)	84.67 ± .829 (3)			[illegible] 80 ± 5.27 (3)			75.25 ± .950 (2)		
HEART		123.50 ± 11.[illegible] (3)	117.33 ± 16.8 (3)			116.70 ± 13.4 (3)			98.05 ± 1.85 (2)		
KIDNEYS	*	68.43 ± 8.7[illegible] (3)	58.70 ± 5.95 (3)		*	63.70 ± .700 (3)			65.30 ± .300 (2)		*
LIVER		649.67 ± 21.3 (3)	352.07 ± 13.8 (3)			359.10 ± 18.9 (3)			562.15 ± 39.2 (2)		
SPLEEN		32.00 ± 4.32 (3)	40.97 ± 10.8 (3)			44.80 ± 16.0 (3)			49.55 ± 9.25 (2)		
GONADS	*	19.10 ± 2.55 (3)	18.77 ± .498 (3)		*	18.83 ± .636 (3)		*	14.90 ± 7.30 (2)		*
ADRENAL		1.40 ± .252 (3)	1.37 ± .120 (3)			1.30 ± .208 (3)			2.00 ± .600 (2)		
THYROID		.97 ± .167 (3)	1.13 ± .203 (3)			1.13 ± .120 (3)			1.30 ± 0.00 (2)		
BRAIN/BODY		7.45 ± .306 (3)	7.62 ± .675 (3)			7.67 ± .503 (3)			7.73 ± .296 (2)		
HEART/BODY		10.96 ± 1.25 (3)	10.30 ± .572 (3)			10.35 ± .767 (3)			10.06 ± .068 (2)		
KIDNEY/BODY		5.95 ± .497 (3)	5.20 ± .315 (3)			5.72 ± .407 (3)			6.70 ± .203 (2)		
LIVER/BODY		39.74 ± 2.05 (3)	34.17 ± 2.04 (3)			32.33 ± 3.41 (3)			57.59 ± 2.54 (2)	*	A
SPLEEN/BODY		2.79 ± .217 (3)	3.52 ± .587 (3)			3.90 ± 1.22 (3)			5.11 ± 1.08 (2)		
GONADS/BODY		1.67 ± .117 (3)	1.68 ± .106 (3)			1.69 ± .159 (3)			1.51 ± .710 (2)		
ADRENAL/BODY		.12 ± .014 (3)	.12 ± .017 (3)			.12 ± .022 (3)			.21 ± .067 (2)		D
THYROID/BODY		.08 ± .009 (3)	.10 ± .011 (3)		A	.10 ± .015 (3)		B	.13 ± .003 (2)		D
HEART/BRAIN		1.47 ± .123 (3)	1.39 ± .206 (3)			1.35 ± .085 (3)			1.30 ± .041 (2)		
KIDNEY/BRAIN		.81 ± .082 (3)	.69 ± .070 (3)			.75 ± .049 (3)			.87 ± .007 (2)		
LIVER/BRAIN		5.34 ± .20[illegible] (3)	4.51 ± .164 (3)			4.20 ± .247 (3)			7.48 ± .615 (2)	*	A
SPLEEN/BRAIN		.38 ± .043 (3)	.49 ± .130 (3)			.50 ± .150 (3)			.66 ± .115 (2)		
GONADS/BRAIN		.23 ± .024 (3)	.22 ± .097 (3)			.22 ± .015 (3)			.20 ± .099 (2)		A
ADRENAL/BRAIN		.02 ± .003 (3)	.02 ± .002 (3)			.02 ± .003 (3)			.03 ± .009 (2)		D
THYROID/BRAIN		.01 ± .002 (3)	.01 ± .002 (3)		A	.01 ± .001 (3)		A	.02 ± .000 (2)		D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D, RATIO TEST CANNOT BE CALCULATED - * .

TABLE 180

EFFECTS OF LAP ON ORGAN WEIGHTS (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE DOGS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
FINAL WEIGHT (KG)		10.23 ± .328 (3)	9.47 ± .769 (3)		9.23 ± .328 (3)		9.95 ± .050 (2)	
BRAIN		84.47 ± 1.91 (3)	82.67 ± 3.22 (3)		72.00 ± 1.06 (3)	*	82.80 ± 3.90 (2)	
HEART		97.90 ± 4.05 (3)	89.53 ± 8.65 (3)		83.23 ± 6.60 (3)		91.85 ± 1.75 (2)	
KIDNEYS		43.17 ± .561 (3)	47.60 ± 3.76 (3)		46.77 ± 1.22 (3)		55.55 ± .950 (2)	
LIVER		365.03 ± 20.1 (3)	383.60 ± 46.8 (3)		366.47 ± 25.8 (3)		578.20 ± 52.8 (2)	* A
SPLEEN		56.77 ± 8.69 (3)	71.37 ± 3.76 (3)		39.87 ± 8.82 (3)		56.65 ± 7.25 (2)	
GONADS		1.43 ± .338 (3)	1.53 ± .273 (3)		.87 ± .120 (3)		.95 ± .250 (2)	
ADRENAL		1.37 ± .088 (3)	1.50 ± .208 (3)		1.40 ± 0.00 (3)		1.75 ± .050 (2)	
THYROID		1.23 ± .088 (3)	.97 ± .067 (3)		1.07 ± .120 (3)		.80 ± .100 (2)	A
BRAIN/BODY		8.27 ± .286 (3)	8.79 ± .412 (3)		7.82 ± .364 (3)		8.32 ± .350 (2)	
HEART/BODY		9.57 ± .315 (3)	9.45 ± .409 (3)		9.00 ± .541 (3)		9.23 ± .130 (2)	
KIDNEY/BODY		4.82 ± .188 (3)	5.03 ± .114 (3)		5.07 ± .139 (3)		5.58 ± .123 (2)	
LIVER/BODY		35.79 ± 2.65 (3)	40.28 ± 1.66 (3)		39.62 ± 1.66 (3)		58.14 ± 5.60 (2)	+ B
SPLEEN/BODY		5.56 ± .840 (3)	7.58 ± .317 (3)		4.30 ± .899 (3)		5.70 ± .757 (2)	
GONADS/BODY		.14 ± .039 (3)	.16 ± .025 (3)	A	.09 ± .012 (3)	B	.10 ± .025 (2)	B
ADRENAL/BODY		.13 ± .011 (3)	.16 ± .010 (3)	A	.15 ± .006 (3)	A	.18 ± .004 (2)	B
THYROID/BODY		.12 ± .009 (3)	.10 ± .001 (3)	A	.12 ± .012 (3)		.08 ± .010 (2)	B
HEART/BRAIN		1.16 ± .069 (3)	1.08 ± .062 (3)		1.16 ± .110 (3)		1.11 ± .031 (2)	
KIDNEY/BRAIN		.58 ± .020 (3)	.57 ± .023 (3)		.65 ± .017 (3)	A	.67 ± .043 (2)	A
LIVER/BRAIN		4.32 ± .173 (3)	4.61 ± .384 (3)		5.10 ± .435 (3)		7.03 ± .969 (2)	* A
SPLEEN/BRAIN		.67 ± .099 (3)	.86 ± .012 (3)		.55 ± .117 (3)		.69 ± .120 (2)	
GONADS/BRAIN		.02 ± .004 (3)	.02 ± .003 (3)		.01 ± .002 (3)	B	.01 ± .003 (2)	B
ADRENAL/BRAIN		.02 ± .001 (3)	.02 ± .002 (3)	A	.02 ± .000 (3)	B	.02 ± .000 (2)	B
THYROID/BRAIN		.01 ± .001 (3)	.01 ± .000 (3)	B	.01 ± .002 (3)		.01 ± .001 (2)	B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R - TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 181

EFFECTS OF LAP ON ORGAN WEIGHT (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE DOGS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

		TREATMENT GROUPS		
DEPENDENT VARIABLES	CONTROL GROUP	0.5 MG/KG/DAY	5.0 MG/KG/DAY	50.0 MG/KG/DAY
FINAL WEIGHT (KG)	7.90	10.50	10.50	10.60
BRAIN	89.60	89.10	76.80	79.90
THYROID	1.09	.95	.98	1.00
HEART	63.90	107.60	95.00	98.30
LIVER	243.70	349.10	310.90	371.80
SPLEEN	16.00	25.70	24.10	28.00
ADRENAL	1.35	1.36	1.77	1.48
KIDNEYS	40.40	52.10	53.70	67.00
TESTES	12.90	22.30	15.20	10.80
BRAIN/BODY WT.	11.34	8.49	7.31	7.54
THYROID/BODY WT.	.14	.09	.09	.09
HEART/BODY WT.	8.09	10.25	9.05	9.27
LIVER/BODY WT.	30.85	33.25	29.61	35.08
SPLEEN/BODY WT.	2.03	2.45	2.30	2.64
ADRENAL/BODY WT.	.17	.13	.17	.14
KIDNEYS/BODY WT.	5.11	4.96	5.11	6.32
TESTES/BODY WT.	1.63	2.12	1.45	1.02
THYROID/BRAIN	.01	.01	.01	.01
HEART/BRAIN	.71	1.21	1.24	1.23
LIVER/BRAIN	2.72	3.92	4.05	4.65
SPLEEN/BRAIN	.18	.29	.31	.35
ADRENAL/BRAIN	.02	.02	.02	.02
KIDNEYS/BRAIN	.45	.58	.70	.84
TESTES/BRAIN	.14	.25	.20	.14

ONE DOG IN EACH GROUP
LAP WAS ADMINISTERED DAILY BY CAPSULE

TABLE 132

EFFECTS OF LAP ON ORGAN WEIGHT (G),
ORGAN-TO-BODY WEIGHT RATIOS (G/KG) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE DOGS AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLES	CONTROL GROUP	TREATMENT GROUPS 0.5 MG/KG/DAY	5.0 MG/KG/DAY	50.0 MG/KG/DAY
FINAL WEIGHT (KG)	9.20	10.20	12.20	9.10
BRAIN	85.80	82.00	86.30	76.00
THYROID	.88	1.13	.96	1.12
HEART	88.20	99.50	95.60	97.70
LIVER	315.00	291.00	371.90	305.90
SPLEEN	49.90	43.30	35.60	27.70
ADRENAL	1.04	1.36	1.31	2.20
KIDNEYS	40.00	45.00	47.20	49.00
GONADS	.79	.96	1.50	.61
BRAIN/BODY WT.	9.33	8.04	7.07	8.35
THYROID/BODY WT.	.10	.11	.08	.12
HEART/BODY WT.	9.59	9.75	7.84	10.74
LIVER/BODY WT.	34.24	28.53	30.48	33.62
SPLEEN/BODY WT.	5.42	4.25	2.92	3.04
ADRENAL/BODY WT.	.11	.13	.11	.24
KIDNEYS/BODY WT.	4.35	4.41	3.87	5.38
GONADS/BODY WT.	.09	.09	.12	.07
THYROID/BRAIN	.01	.01	.01	.01
HEART/BRAIN	1.03	1.21	1.11	1.29
LIVER/BRAIN	3.67	3.55	4.31	4.02
SPLEEN/BRAIN	.58	.53	.41	.36
ADRENAL/BRAIN	.01	.02	.02	.03
KIDNEYS/BRAIN	.47	.55	.55	.64
GONADS/BRAIN	.01	.01	.02	.01

ONE DOG IN EACH GROUP
LAP WAS ADMINISTERED DAILY BY CAPSULE

TABLE 183

HEMATOLOGY OF MALF DOGS BEFORE TREATMENT WITH LAP

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
RBC (X 10^6)		5.86 ± .094 (5)	6.14 ± .280 (5)		6.17 ± .247 (5)		6.07 ± .181 (5)	
HGB (G %)		13.96 ± .189 (5)	14.39 ± .558 (5)		14.64 ± .534 (5)		14.20 ± .412 (5)	
HCT (%)		40.54 ± .508 (5)	41.66 ± 1.62 (5)		42.62 ± 1.52 (5)		41.66 ± 1.71 (5)	
MCV $(U)^3$		69.40 ± .748 (5)	68.20 ± .860 (5)		69.60 ± .812 (5)		68.60 ± .812 (5)	
MCH (UUG)		23.66 ± .197 (5)	23.16 ± .383 (5)		23.56 ± .234 (5)		23.20 ± .228 (5)	
MCHC (%)		34.32 ± .132 (5)	34.22 ± .116 (5)		34.22 ± .229 (5)		33.98 ± .107 (5)	
WBC (X 10^3)		10.16 ± .695 (5)	11.34 ± .943 (5)		11.88 ± .918 (5)		10.76 ± .805 (5)	
PMN (%)		51.40 ± 2.96 (5)	53.60 ± 3.49 (5)		50.60 ± 2.11 (5)		52.20 ± 2.44 (5)	
BANDS (%)		2.20 ± .800 (5)	6.40 ± 2.01 (5)	*	3.00 ± 1.76 (5)	•	3.00 ± 1.30 (5)	•
LYMPH (%)		30.60 ± .927 (5)	30.80 ± 3.99 (5)		33.20 ± 2.94 (5)		31.80 + 4.31 (5)	
MONO (%)		7.00 ± .633 (5)	2.60 ± .927 (5)	A	5.20 ± 1.85 (5)		4.00 ± 1.92 (5)	
EOSIN (%)		8.80 ± 3.01 (5)	6.60 ± 1.75 (5)		8.00 ± 2.86 (5)		9.00 ± 3.41 (5)	
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	
RETICS (%)	*	.30 ± .089 (5)	.86 ± .277 (5)		.26 ± .108 (5)		.44 ± .051 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 184

HEMATOLOGY OF FEMALE DOGS BEFORE TREATMENT WITH LAP

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T	R	5.0 MG/KG/DAY	T	R	50 MG/KG/DAY	T	R
RBC (X 10^6)		7.04 ± .355 (5)	6.43 ± .094 (5)			6.91 ± .202 (5)			6.52 ± .164 (5)		
HGB (G %)		16.70 ± .721 (5)	15.28 ± .211 (5)			16.12 ± .353 (5)			15.50 ± .332 (5)		
HCT (%)		48.20 ± 1.97 (5)	44.64 ± .595 (5)			46.50 ± .888 (5)			45.10 ± .998 (5)		
MCV $(U)^3$		69.00 ± 1.05 (5)	69.60 ± .245 (5)			68.00 ± 1.00 (5)			69.40 ± .748 (5)		
MCH (UUG)		23.50 ± .321 (5)	23.56 ± .093 (5)			23.20 ± .241 (5)			23.58 ± .285 (5)		
MCHC (%)		34.46 ± .234 (5)	34.10 ± .123 (5)			34.54 ± .129 (5)			34.22 ± .097 (5)		
WBC (X 10^3)		10.82 ± 1.21 (5)	10.88 ± 1.03 (5)			10.36 ± .748 (5)			12.78 ± 1.15 (5)		
PMN (%)		56.60 ± 4.12 (5)	60.60 ± 1.29 (5)			61.80 ± 2.75 (5)			60.40 ± 3.53 (5)		
BANDS (%)		1.20 ± .735 (5)	3.20 ± 1.83 (5)		•	3.60 ± 1.69 (5)		•	3.60 ± 1.29 (5)		•
LYMPH (%)		31.60 ± 4.34 (5)	25.40 ± 1.03 (5)			26.00 ± 2.51 (5)			28.80 ± 3.68 (5)		
MONO (%)		7.60 ± 1.36 (5)	5.20 ± 1.43 (5)			2.60 ± 1.40 (5)		B	3.80 ± 1.74 (5)		
EOSIN (%)		3.00 ± .894 (5)	5.60 ± 1.29 (5)			6.00 ± .949 (5)			3.40 ± .748 (5)		
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)			0.00 ± 0.00 (5)			0.00 ± 0.00 (5)		
RETICS (%)		.26 ± .103 (5)	.12 ± .080 (5)			.18 ± .066 (5)			.44 ± .197 (5)		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 185

EFFECTS OF LAP ON HEMATOLOGY
OF MALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	.5 MG/KG/DAY (TREATMENT GROUPS)	T R	5.0 MG/KG/DAY (TREATMENT GROUPS)	T R	50 MG/KG/DAY (TREATMENT GROUPS)	T R
RBC (X 10^6)	*	6.04 ± .105 (5)	6.10 ± .288 (5)		5.82 ± .181 (5)		4.65 ± .475 (5)	
HGB (G %)		14.24 ± .299 (5)	14.24 ± .530 (5)		13.98 ± .460 (5)		10.94 ± 1.07 (5)	* A
HCT (%)		41.54 ± .838 (5)	41.64 ± 1.60 (5)		41.50 ± 1.18 (5)		33.30 ± 2.77 (5)	*
MCV $(U)^3$		69.80 ± 1.11 (5)	69.40 ± .927 (5)		72.40 ± .812 (5)		72.60 ± 1.81 (5)	
MCH (UUG)		23.32 ± .269 (5)	23.14 ± .393 (5)		23.80 ± .321 (5)		23.32 ± .340 (5)	
MCHC (%)	*	34.12 ± .136 (5)	34.02 ± .097 (5)		33.50 ± .167 (5)	*	32.62 ± .562 (5)	
WBC (X 10^3)		12.54 ± 1.35 (5)	16.96 ± 2.47 (5)		14.74 ± .900 (5)		19.32 ± 3.30 (5)	
PMN (%)		52.20 ± 2.46 (5)	66.20 ± 5.14 (5)		62.20 ± 3.80 (5)		70.00 ± 4.30 (5)	
BANDS (%)	*	.40 ± .245 (5)	3.40 ± 1.57 (5)	*	2.60 ± .927 (5)	*	1.80 ± .860 (5)	*
LYMPH (%)		25.60 ± 2.56 (5)	22.60 ± 4.53 (5)		23.60 ± 4.73 (5)		19.80 ± 1.93 (5)	
MONO (%)		7.00 ± .949 (5)	3.20 ± [illegible].11 (5)		5.60 ± 1.33 (5)		4.80 ± 2.01 (5)	
EOSIN (%)		14.80 ± 2.40 (5)	4.00 ± 1.14 (5)	* C	6.00 ± 1.82 (5)	B	3.60 ± 3.12 (5)	* C
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	
RETICS (%)	+	.44 ± .075 (5)	.36 ± .108 (5)		1.28 ± .171 (5)	* A	5.04 ± 2.73 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 186

EFFECTS OF LAP ON HEMATOLOGY
OF FEMALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
RBC (X 10^6)		6.93 ± .262 (5)	6.16 ± .186 (5)		6.31 ± .213 (5)		4.11 ± .118 (5)	
HGB (G %)		16.24 ± .500 (5)	14.66 ± .479 (5)		14.84 ± .450 (5)		9.84 ± .363 (5)	+ B
HCT (%)		47.08 ± 1.44 (5)	42.90 ± 1.38 (5)		44.10 ± 1.33 (5)		30.58 ± .963 (5)	+ B
MCV $(U)^3$	*	69.40 ± .927 (5)	70.80 ± .200 (5)		71.20 ± 1.07 (5)		75.00 ± 1.73 (5)	
MCH (UUG)		23.20 ± .351 (5)	23.50 ± .114 (5)		23.28 ± .289 (5)		23.86 ± .543 (5)	
MCHC (%)		34.24 ± .199 (5)	33.92 ± .074 (5)		33.44 ± .172 (5)	*	32.22 ± .206 (5)	+
WBC (X 10^3)		12.00 ± .957 (5)	14.44 ± 1.45 (5)		15.24 ± 1.15 (5)		16.60 ± 1.56 (5)	
PMN (%)		62.20 ± 5.18 (5)	66.60 ± 4.92 (5)		58.80 ± 2.58 (5)		71.00 ± 4.01 (5)	
BANDS (%)	*	.60 ± .600 (5)	3.00 ± 1.10 (5)	•	.80 ± .583 (5)	•	6.60 ± 2.32 (5)	•
LYMPH (%)		22.00 ± 4.18 (5)	21.00 ± 4.80 (5)		29.20 ± 5.07 (5)		19.00 ± 4.06 (5)	
MONO (%)		7.80 ± .800 (5)	3.60 ± 1.08 (5)	B	5.60 ± 1.57 (5)		3.40 ± .510 (5)	B
EOSIN (%)	*	7.40 ± 1.21 (5)	5.40 ± 1.44 (5)		5.60 ± 2.34 (5)		0.00 ± 0.00 (5)	* D
BASO (%)		0.00 ± 0.00 (5)	0.00 ± 0.00 (5)		0.00 ± 0.00 (5)		0.00 ± 0.00 (5)	
RETICS (%)	+	.20 ± .063 (5)	.46 ± .040 (5)	* •	.86 ± .172 (5)	*	3.52 ± .954 (5)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETT. CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 187

EFFECTS OF LAP ON HEMATOLOGY
OF HALF DOGS AFTER 8 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T	R	5.0 MG/KG/DAY	T	R	50 MG/KG/DAY	T	R
RBC (X 10^6)		6.17 ± .164 (3)	5.99 ± .416 (3)			5.99 ± .203 (3)			4.41 ± .040 (2)		
HGB (G %)		14.77 ± .338 (3)	13.93 ± .694 (3)			14.40 ± .436 (3)			10.85 ± .350 (2)	+	A
HCT (%)		42.80 ± 1.00 (3)	40.80 ± 2.04 (3)			42.97 ± 1.22 (3)			32.70 ± 1.30 (2)	*	A
MCV (U)3		69.00 ± 1.53 (3)	68.00 ± 1.00 (3)			71.33 ± .882 (3)			73.00 ± 2.00 (2)		
MCH (UUG)		23.87 ± .371 (3)	23.23 ± .524 (3)			23.87 ± .120 (3)			24.45 ± .650 (2)		
MCHC (%)		34.47 ± .145 (3)	34.27 ± .318 (3)			33.47 ± .219 (3)			33.25 ± .250 (2)		
WBC (X 10^3)		10.59 ± .889 (3)	12.23 ± .348 (3)			14.07 ± 2.00 (3)			18.90 ± 1.60 (2)		
PMN (%)		62.00 ± 1.53 (3)	57.00 ± 3.61 (3)			61.67 ± 4.18 (3)			75.50 ± 7.50 (2)		
BANDS (%)		1.67 ± 1.67 (3)	2.00 ± 1.00 (3)		•	.67 ± .667 (3)		•	2.50 ± .500 (2)		•
LYMPH (%)		23.00 ± 1.73 (3)	28.67 ± 2.73 (3)			26.67 ± 3.84 (3)			13.00 ± 5.00 (2)		
MONO (%)		4.67 ± 2.33 (3)	2.33 ± .882 (3)			7.67 ± .333 (3)			6.00 ± 1.00 (2)		
EOSIN (%)		8.67 ± 1.67 (3)	9.67 ± .333 (3)			3.33 ± .333 (3)		B	3.00 ± 2.00 (2)		B
BASO (%)		0.00 ± 0.00 (3)	.33 ± .333 (3)		•	0.00 ± 0.00 (3)		•	0.00 ± 0.00 (2)		•
RETICS (%)	*	.30 ± .252 (3)	.50 ± .100 (3)		•	.17 ± .033 (3)		•	1.90 ± 1.50 (2)		•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 188

EFFECTS OF LAP ON HEMATOLOGY
OF FEMALE DOGS AFTER 8 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
RBC (X 10^6)		6.42 ± .375 (3)	6.24 ± .145 (3)		6.22 ± .059 (3)		5.44 ± .218 (3)	
HGB (G %)		15.63 ± .845 (3)	14.90 ± .300 (3)		14.63 ± .260 (3)		13.07 ± .926 (3)	
HCT (%)		44.90 ± 2.54 (3)	43.53 ± 1.08 (3)		43.13 ± .835 (3)		40.57 ± 1.66 (3)	
MCV (U)^3		69.67 ± 1.86 (3)	69.33 ± .333 (3)		69.00 ± 1.15 (3)		73.33 ± 1.45 (3)	
MCH (UUG)		24.17 ± .636 (3)	23.67 ± .088 (3)		23.37 ± .219 (3)		24.03 ± .935 (3)	
MCHC (%)		34.70 ± .115 (3)	34.20 ± .208 (3)		33.93 ± .338 (3)		32.50 ± .721 (3)	*
WBC (X 10^3)		10.40 ± .896 (3)	14.43 ± .977 (3)		13.93 ± 1.16 (3)		16.10 ± .862 (3)	
PMN (%)		53.67 ± 5.67 (3)	66.67 ± 2.91 (3)		67.00 ± 5.00 (3)		73.67 ± 5.46 (3)	
BANDS (%)		1.00 ± 1.00 (3)	3.33 ± 1.20 (3)	•	1.00 ± 0.00 (3)	•	1.00 ± .577 (3)	•
LYMPH (%)		32.67 ± 4.33 (3)	22.00 ± 1.15 (3)		21.67 ± 4.98 (3)		18.33 ± 6.57 (3)	
MONO (%)		5.33 ± .882 (3)	5.00 ± 1.00 (3)		6.67 ± 1.20 (3)		6.33 ± .333 (3)	
EOSIN (%)		7.33 ± 1.76 (3)	3.00 ± 1.15 (3)	A	3.67 ± .882 (3)		.67 ± .333 (3)	* D
BASO (%)		0.00 ± 0.00 (3)	0.00 ± 0.00 (3)	•	1.33 ± 1.33 (3)	•	0.00 ± 0.00 (3)	•
RETICS (%)		.10 ± .058 (3)	.47 ± .371 (3)	•	.17 ± .120 (3)	•	2.53 ± .467 (3)	+ •

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 189

EFFECTS OF LAP ON HEMATOLOGY
OF MALE DOGS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
RBC (X 10^6)		6.26 ± .092 (3)	5.99 ± .518 (3)		6.02 ± .382 (3)		4.81 ± .675 (2)	
HGB (G %)		15.03 ± .291 (3)	13.87 ± .991 (3)		14.40 ± .907 (3)		12.15 ± 1.35 (2)	
HCT (%)		43.17 ± .617 (3)	40.63 ± 2.75 (3)		43.27 ± 2.82 (3)		36.90 ± 4.30 (2)	
MCV (U)^3		68.67 ± 1.20 (3)	68.00 ± 1.00 (3)		70.67 ± .882 (3)		74.50 ± 3.50 (2)	
MCH (UUG)		23.87 ± .470 (3)	23.07 ± .410 (3)		23.80 ± .231 (3)		25.40 ± .600 (2)	
MCHC (%)		34.70 ± .115 (3)	34.03 ± .233 (3)		33.33 ± .291 (3)	*	33.40 ± .260 (2)	*
WBC (X 10^3)		10.47 ± .536 (3)	11.73 ± .601 (3)		14.10 ± 2.87 (3)		19.35 ± .750 (2)	
PMN (%)		51.67 ± 3.84 (3)	48.33 ± 3.53 (3)		62.33 ± 1.20 (3)		76.00 ± 1.00 (2)	+ B
BANDS (%)		.67 ± .333 (3)	0.00 ± 0.00 (3)	*	1.00 ± 1.00 (3)	*	1.00 ± 1.00 (2)	*
LYMPH (%)		31.00 ± 2.89 (3)	32.00 ± 6.00 (3)		29.67 ± 1.45 (3)		18.00 ± 1.00 (2)	
MONO (%)		7.00 ± 1.15 (3)	6.67 ± 1.76 (3)		2.33 ± .333 (3)	B	1.50 ± .500 (2)	B
EOSIN (%)		9.67 ± 3.48 (3)	13.00 ± 6.11 (3)		4.67 ± 1.20 (3)		3.50 ± .500 (2)	
BASO (%)		0.00 ± 0.00 (3)	0.00 ± 0.00 (3)		0.00 ± 0.00 (3)		0.00 ± 0.00 (2)	
RETICS (%)		.60 ± .231 (3)	.57 ± .167 (3)		1.53 ± .088 (3)		3.35 ± .550 (2)	+

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLF 190

EFFECTS OF LAP ON HEMATOLOGY
OF FEMALE DOGS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T	R	5.0 MG/KG/DAY	T	R	50 MG/KG/DAY	T	R
RBC (X 10^6)		6.59 ± .244 (3)	6.28 ± .299 (3)			6.37 ± .188 (3)			5.78 ± .475 (2)		
HGB (G %)		16.03 ± .736 (3)	14.9[illegible] ± .636 (3)			15.03 ± .593 (3)			14.90 ± 1.80 (2)		
HCT (%)		46.03 ± 1.79 (3)	43.57 ± 1.97 (3)			44.17 ± 1.52 (3)			44.95 ± 5.45 (2)		
MCV (U)^3		70.00 ± 1.53 (3)	69.00 ± .577 (3)			68.67 ± 1.20 (3)			77.00 ± 3.00 (2)		
MCH (UUG)		24.23 ± .578 (3)	23.60 ± .115 (3)			23.50 ± .300 (3)			25.50 ± 1.00 (2)		
MCHC (%)		34.70 ± .265 (3)	34.17 ± .233 (3)			34.07 ± .367 (3)			33.05 ± .050 (2)	*	
WBC (X 10^3)		10.87 ± 1.83 (3)	12.17 ± .869 (3)			11.83 ± .167 (3)			19.20 ± 2.60 (2)		
PMN (%)		57.67 ± 2.03 (3)	58.00 ± 2.89 (3)			68.33 ± 3.76 (3)			61.50 ± 5.50 (2)		
BANDS (%)		.67 ± .333 (3)	1.67 ± .333 (3)		•	1.00 ± .577 (3)		•	1.00 ± 1.00 (2)		•
LYMPH (%)		29.33 ± 4.48 (3)	27.33 ± 3.48 (3)			24.00 ± 1.53 (3)			23.50 ± 1.50 (2)		
MONO (%)		4.67 ± 1.45 (3)	5.33 ± 2.03 (3)			2.33 ± 1.86 (3)			4.50 ± 2.50 (2)		
EOSIN (%)		7.67 ± 2.19 (3)	7.67 ± 1.45 (3)			4.00 ± 1.00 (3)			9.50 ± 5.50 (2)		
BASO (%)		0.00 ± 0.00 (3)	0.00 ± 0.00 (3)			0.00 ± 0.00 (3)			0.00 ± 0.00 (2)		
RETICS (%)	*	.47 ± .067 (3)	.37 ± .088 (3)		•	1.17 ± .145 (3)	*	•	6.25 ± 1.55 (2)		•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : *CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A*
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 191

EFFECTS OF LAP ON HEMATOLOGY OF MALE DOGS
AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLES	CONTROL GROUP	TREATMENT GROUPS 0.5 MG/KG/DAY	5.0 MG/KG/DAY	50.0 MG/KG/DAY
RBC (X 10^6)	25.7	9.9	13.5	10.0
HGB (G %)	5.90	6.37	5.94	6.18
HCT (%)	13.7	14.2	14.7	14.3
MCV $(U)^3$	40.3	41.5	42.8	42.5
MCH (UUG)	68	65	72	68
MCHC (%)	23.3	22.1	24.5	23.0
WBC (X 10^3)	34.1	34.1	34.3	33.5
PMN (%)	77	53	61	50
BANDS (%)	8	0	2	0
LYMPH (%)	9	28	22	35
MONO (%)	1	5	4	8
EOSIN (%)	5	14	11	7
BASO (%)	0	0	0	0
RETICS (%)	0.8	0.0	0.6	0.2

ONE DOG IN EACH GROUP
LAP WAS ADMINISTERED DAILY BY CAPSULE

TABLE 192

EFFECTS OF LAP ON HEMATOLOGY OF FEMALE DOGS
AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLES	CONTROL GROUP	TREATMENT GROUPS 0.5 MG/KG/DAY	3.0 MG/KG/DAY	50.0 MG/KG/DAY
RBC (X 10^6)	12.6	11.9	9.8	7.5
HGB (G %)	6.95	6.32	6.03	5.67
HCT (%)	16.1	15.2	14.7	13.1
MCV $(U)^3$	46.3	44.2	42.8	39.0
MCH (UUG)	67	69	70	68
MCHC (%)	23.1	23.8	24.0	23.0
WBC (X 10^3)	34.9	34.4	34 4	33.6
PMN (%)	56	68	55	53
BANDS (%)	0	0	0	0
LYMPH (%)	34	17	40	39
MONO (%)	6	9	3	1
EOSIN (%)	4	6	2	7
BASO (%)	0	0	0	0
RETICS (%)	0.0	0.0	0.0	0.1

ONE DOG IN EACH GROUP
LAP WAS ADMINISTERED DAILY BY CAPSULE

TABLE 193

CLINICAL CHEMISTRY OF MALE DOGS BEFORE TREATMENT WITH LAP

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
GLUCOSE (MG %)	*	100.40 ± 6.35 (5)	108.20 ± 5.51 (5)		107.80 ± 2.80 (5)		103.40 ± .927 (5)	
BUN (MG %)		16.20 ± 1.56 (5)	14.20 ± 2.06 (5)		12.80 ± .653 (5)		13.00 ± 1.10 (5)	
CREAT (MG %)		.74 ± .024 (5)	.74 ± .051 (5)		.72 ± .020 (5)		.66 ± .024 (5)	A
URIC ACID (MG)	*	.38 ± .037 (5)	.42 ± .020 (5)		.20 ± .084 (5)		.68 ± .116 (5)	
NA (MEQ/L)		145.00 ± .633 (5)	145.60 ± .678 (5)		145.80 ± .735 (5)		146.20 ± .735 (5)	
K (MEQ/L)		4.82 ± .092 (5)	4.90 ± .105 (5)		5.18 ± .220 (5)		4.84 ± .150 (5)	
CO_2 (MEQ/L)		21.00 ± .316 (5)	22.00 ± .548 (5)		22.20 ± .800 (5)		22.80 ± .374 (5)	
CL (MEQ/L)		113.40 ± .678 (5)	113.40 ± 1.08 (5)		112.80 ± .583 (5)		112.80 ± .490 (5)	
CA (MG %)		10.32 ± .136 (5)	10.56 ± .178 (5)		10.36 ± .227 (5)		10.54 ± .103 (5)	
P (MG %)		5.06 ± .229 (5)	4.82 ± .159 (5)		5.06 ± .189 (5)		4.98 ± .325 (5)	
NA-(CL+CO_2)		10.60 ± .510 (5)	10.20 ± .583 (5)		10.80 ± .583 (5)		10.60 ± .678 (5)	
CHOL (MG %)		155.20 ± 17.5 (5)	157.20 ± 11.2 (5)		143.60 ± 17.2 (5)		160.00 ± 10.2 (5)	
TRIG (MG %)		28.00 ± 3.03 (5)	34.60 ± 7.47 (5)		38.80 ± 8.10 (5)		[illegible].80 ± 6.09 (5)	
BILI (MG %)		.12 ± .020 (5)	.10 ± 0.00 (5)	A	.10 ± 0.00 (5)	A	.10 ± 0.00 (5)	A
SGOT (MU/ML)	*	43.60 ± 2.25 (5)	43.00 ± 5.55 (5)		33.00 ± 1.30 (5)	* A	37.40 ± 1.96 (5)	
SGPT (MU/ML)	+	44.20 ± 3.69 (5)	55.60 ± 21.4 (5)		38.00 ± 2.19 (5)		185.60 ± 91.3 (5)	
LDH (MU/ML)		74.60 ± 6.02 (5)	51.20 ± 7.31 (5)		51.40 ± 7.04 (5)		72.20 ± 13.1 (5)	
ALK-P (MU/ML)		127.80 ± 17.0 (5)	144.80 ± 21.5 (5)		108.50 ± 17.2 (5)		125.80 ± 19.2 (5)	
IRON (MCG %)		271.60 ± 16.3 (5)	187.00 ± 23.6 (5)		156.40 ± 31.2 (5)	* B	192.40 ± 20.7 (5)	
PROTEIN (GM %)		5.72 ± .146 (5)	5.74 ± .098 (5)		5.60 ± .161 (5)		5.72 ± .080 (5)	
ALBUMIN (GM %)		2.80 ± .063 (5)	2.78 ± .049 (5)		2.62 ± .107 (5)		2.86 ± .051 (5)	
GLOBULIN (GM%)		2.92 ± .116 (5)	2.96 ± .068 (5)		2.88 ± .107 (5)		2.86 ± .068 (5)	
A/G RATIO		.97 ± .038 (5)	.94 ± .020 (5)		.95 ± .029 (5)		1.00 ± .029 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - *

TABLF 194

CLINICAL CHFMISTRY OF FF4ALF DOGS BFFORE TRFATMFNT WITH LAP

DEPFNDENT VARIABLE	B C	CONTROL GROUP	.5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
			TREATMENT GROUPS					
GLUCOSE (MG %)		98.60 ± 3.70 (5)	110.00 ± 4.23 (5)		99.00 ± 2.74 (5)		107.80 ± 2.18 (5)	
BUN (MG %)		13.40 ± 1.36 (5)	11.40 ± .600 (5)		12.40 ± .872 (5)		11.80 ± .735 (5)	
CREAT (MG %)		.72 ± .037 (5)	.78 ± .037 (5)		.76 ± .024 (5)		.66 ± .040 (5)	
URIC ACID (MG)		.60 ± .084 (5)	.32 ± .020 (5)	B	.22 ± .092 (5)	* C	.42 ± .049 (5)	
NA (MEQ/L)		147.00 ± .447 (5)	146.80 ± .374 (5)		145.80 ± .490 (5)		148.00 ± 1.05 (5)	
K (MEQ/L)		4.74 ± .172 (5)	4.62 ± .107 (5)		4.94 ± .140 (5)		4.72 ± .074 (5)	
CO_2 (MEQ/L)		21.20 ± .970 (5)	22.40 ± .400 (5)		24.20 ± .490 (5)	*	23.00 ± .707 (5)	
CL (MEQ/L)		112.40 ± .980 (5)	112.40 ± .400 (5)		111.00 ± .633 (5)		112.40 ± .927 (5)	
CA (MG %)		10.90 ± .032 (5)	10.70 ± .084 (5)		10.64 ± .087 (5)		10.96 ± .075 (5)	
P (MG %)		5.36 ± .268 (5)	4.84 ± .199 (5)		4.36 ± .140 (5)	*	4.84 ± .166 (5)	
NA-(CL+CO_2)		13.40 ± .678 (5)	12.00 ± .316 (5)		10.60 ± .812 (5)		12.60 ± 1.21 (5)	
CHOL (MG %)		144.40 ± 9.99 (5)	151.20 ± 11.6 (5)		136.40 ± 7.63 (5)		153.20 ± 7.32 (5)	
TRIG (MG %)		24.40 ± 3.08 (5)	21.80 ± 2.91 (5)		31.20 ± 3.97 (5)		31.20 ± 6.39 (5)	
BILI (MG %)		.14 ± .024 (5)	.10 ± 0.00 (5)	B	.10 ± 0.00 (5)	B	.10 ± 0.00 (5)	B
SGOT (MU/ML)		37.40 ± 3.97 (5)	36.00 ± 3.39 (5)		30.80 ± 1.59 (5)		33.40 ± 2.87 (5)	
SGPT (MU/ML)	+	39.60 ± 3.72 (5)	38.00 ± 1.14 (5)		83.00 ± 51.8 (5)		32.00 ± 6.07 (5)	
LDH (MU/ML)	+	106.40 ± 46.4 (5)	75.00 ± 13.0 (5)	•	38.80 ± 2.25 (5)	•	40.60 ± 5.39 (5)	•
ALK-P (MU/ML)	*	103.60 ± 11.1 (5)	117.00 ± 8.45 (5)		94.00 ± 7.92 (5)		126.80 ± 35.0 (5)	
IRON (MCG %)		219.00 ± 18.0 (5)	179.40 ± 11.5 (5)		142.00 ± 22.9 (5)	A	164.00 ± 19.5 (5)	
PROTEIN (GM %)	*	5.88 ± .186 (5)	5.66 ± .040 (5)		5.50 ± .059 (5)		6.00 ± .055 (5)	
ALBUMIN (GM %)		3.10 ± .054 (5)	2.90 ± .032 (5)		2.82 ± .066 (5)		2.98 ± .086 (5)	
GLOBULIN (GM%)		2.78 ± .116 (5)	2.76 ± .040 (5)		2.72 ± .116 (5)		3.02 ± .092 (5)	
A/G RATIO		1.12 ± .030 (5)	1.05 ± .022 (5)		1.06 ± .064 (5)		.99 ± .059 (5)	

ENTRIES ARF MFANS AND STANDARD FRRORS WITH GROUP N IN PARENTHFSFS. LAP ADMINISTERFD DAILY BY CAPSULE
* CONFIDENCF LEVFL = .95
+ CONFIDFNCF LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMFNT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TFST
R = TREATMENT-CONTROL RATIO TFST : CONFIDFNCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATFD - • .

TABLF 195

EFFECTS OF LAP ON CLINICAL CHEMISTRY
OF MALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
GLUCOSE (MG %)		102.40 ± 5.20 (5)	97.80 ± 4.65 (5)		100.60 ± 3.61 (5)		102.20 ± 3.12 (5)	
BUN (MG %)	*	13.80 ± 1.24 (5)	15.80 ± 1.36 (5)		13.60 ± .245 (5)		18.00 ± 2.81 (5)	
CREAT (MG %)		.78 ± .037 (5)	.88 ± .037 (5)	A	.66 ± .040 (5)	A	.52 ± .058 (5)	+ B
URIC ACID (MG)		.32 ± .066 (5)	.54 ± .087 (5)		.54 ± .098 (5)		.48 ± .037 (5)	
NA (MEQ/L)		146.20 ± .583 (5)	145.80 ± .583 (5)		146.20 ± .583 (5)		145.20 ± .735 (5)	
K (MEQ/L)	*	4.78 ± .107 (5)	4.80 ± .089 (5)		4.70 ± .071 (5)		5.42 ± .267 (5)	
CO_2 (MEQ/L)		23.40 ± .748 (5)	22.40 ± .510 (5)		22.80 ± .374 (5)		24.00 ± 1.10 (5)	
CL (MEQ/L)	*	113.20 ± .374 (5)	114.20 ± .374 (5)		113.40 ± .872 (5)		111.80 ± 1.59 (5)	
CA (MG %)		10.48 ± .107 (5)	10.32 ± .146 (5)		10.32 ± .124 (5)		9.98 ± .193 (5)	
P (MG %)		4.62 ± .153 (5)	4.90 ± .167 (5)		4.92 ± .116 (5)		4.96 ± .333 (5)	
NA-(CL+CO_2)		9.60 ± .812 (5)	9.20 ± .374 (5)		10.00 ± .447 (5)		9.40 ± 1.03 (5)	
CHOL (MG %)		152.20 ± 16.3 (5)	156.40 ± 8.58 (5)		147.80 ± 14.7 (5)		157.20 ± 17.4 (5)	
TRIG (MG %)		17.60 ± 2.20 (5)	22.00 ± 2.41 (5)		22.00 ± 5.03 (5)		46.80 ± 7.81 (5)	+
BILI (MG %)		.14 ± .024 (5)	.12 ± .020 (5)	A	.20 ± 0.00 (5)	C	.14 ± .040 (5)	
SGOT (MU/ML)		49.60 ± 3.17 (5)	51.80 ± 1.83 (5)		56.00 ± 3.41 (5)		42.20 ± 2.63 (5)	
SGPT (MU/ML)	+	46.20 ± 1.98 (5)	31.60 ± 3.83 (5)	*	32.80 ± 2.06 (5)	* A	54.20 ± 40.2 (5)	
LDH (MU/ML)		99.80 ± 19.9 (5)	89.80 ± 16.1 (5)		122.80 ± 10.2 (5)		119.80 ± 22.8 (5)	
ALK-P (MU/ML)		121.40 ± 9.44 (5)	151.80 ± 11.6 (5)		101.80 ± 14.5 (5)		103.40 ± 29.6 (5)	
IRON (MCG %)		174.80 ± 18.7 (5)	122.80 ± 9.14 (5)		185.80 ± 18.5 (5)		237.80 ± 24.1 (5)	
PROTEIN (GM %)		5.98 ± .102 (5)	5.92 ± .066 (5)		5.88 ± .124 (5)		5.36 ± .197 (5)	*
ALBUMIN (GM %)		2.84 ± .081 (5)	2.76 ± .087 (5)		2.80 ± .045 (5)		2.72 ± .120 (5)	
GLOBULIN (GM%)		3.14 ± .081 (5)	3.16 ± .068 (5)		3.08 ± .116 (5)		2.64 ± .093 (5)	*
A/G RATIO		.91 ± .039 (5)	.88 ± .041 (5)		.91 ± .037 (5)		1.03 ± .033 (5)	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 196

EFFECTS OF LAP ON CLINICAL CHEMISTRY
OF FEMALE DOGS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
GLUCOSE (MG %)		107.40 ± 4.70 (5)	109.40 ± 2.09 (5)		100.60 ± 2.60 (5)		112.00 ± 4.22 (5)	
BUN (MG %)		14.40 ± .678 (5)	13.40 ± 1.47 (5)		13.60 ± 1.21 (5)		21.80 ± 1.16 (5)	+ B
CREAT (MG %)		.78 ± .086 (5)	.89 ± .032 (5)		.66 ± .051 (5)		.46 ± .024 (5)	+ B
URIC ACID (MG)		.34 ± .121 (5)	.18 ± .049 (5)		.56 ± .068 (5)		.46 ± .040 (5)	
NA (MEQ/L)		148.00 ± .548 (5)	147.20 ± 1.02 (5)		145.80 ± .490 (5)		146.40 ± 1.03 (5)	
K (MEQ/L)		4.66 ± .129 (5)	4.40 ± .155 (5)		4.64 ± .121 (5)		4.96 ± .144 (5)	
CO_2 (MEQ/L)		23.20 ± .970 (5)	22.80 ± .583 (5)		24.20 ± .583 (5)		26.60 ± 1.94 (5)	
CL (MEQ/L)	+	113.80 ± .800 (5)	113.80 ± .735 (5)		112.20 ± .374 (5)		110.20 ± 3.58 (5)	
CA (MG %)	*	10.78 ± .037 (5)	10.54 ± .075 (5)	*	10.74 ± .051 (5)		10.20 ± .192 (5)	*
P (MG %)		4.96 ± .254 (5)	4.62 ± .177 (5)		4.26 ± .147 (5)		4.78 ± .329 (5)	
NA-(CL+CO_2)		11.00 ± .894 (5)	10.60 ± .678 (5)		10.40 ± .510 (5)		9.60 ± 1.08 (5)	
CHOL (MG %)		158.80 ± 17.5 (5)	177.60 ± 18.7 (5)		167.80 ± 16.1 (5)		150.40 ± 16.0 (5)	
TRIG (MG %)	*	21.00 ± 3.36 (5)	21.40 ± 1.72 (5)		30.20 ± 3.37 (5)		54.80 ± 11.3 (5)	*
BILI (MG %)		.16 ± .024 (5)	.20 ± 0.00 (5)	B	.18 ± .020 (5)	A	.16 ± .024 (5)	
SGOT (MU/ML)	*	39.20 ± 2.56 (5)	38.60 ± 2.89 (5)		44.60 ± 2.91 (5)		51.80 ± 8.64 (5)	
SGPT (MU/ML)	*	38.60 ± 6.00 (5)	34.80 ± 1.77 (5)		28.40 ± 2.56 (5)		19.60 ± 1.03 (5)	* B
LDH (MU/ML)		37.20 ± 2.91 (5)	63.00 ± 8.20 (5)		108.80 ± 10.7 (5)	+ D	82.40 ± 7.72 (5)	+ A
ALK-P (MU/ML)	+	97.00 ± 10.3 (5)	127.20 ± 9.59 (5)		106.60 ± 8.63 (5)		128.60 ± 60.7 (5)	
IRON (MCG %)		155.20 ± 23.5 (5)	189.40 ± 17.8 (5)		174.80 ± 21.5 (5)		180.20 ± 47.6 (5)	
PROTEIN (GM %)	*	5.90 ± .032 (5)	5.92 ± .136 (5)		5.90 ± .095 (5)		5.54 ± .172 (5)	
ALBUMIN (GM %)	*	2.98 ± .049 (5)	2.84 ± .024 (5)	*	2.78 ± .037 (5)	*	2.82 ± .156 (5)	
GLOBULIN (GM%)		2.92 ± .074 (5)	3.08 ± .139 (5)		3.12 ± .128 (5)		2.72 ± .136 (5)	
A/G RATIO		1.02 ± .039 (5)	.93 ± .050 (5)		.90 ± .049 (5)		1.05 ± .091 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 197

EFFECTS OF LAP ON CLINICAL CHEMISTRY
OF MALE DOGS AFTER 8 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
GLUCOSE (MG %)	*	101.33 ± 9.53 (3)	100.00 ± 0.00 (3)		97.33 ± 2.91 (3)		88.50 ± 1.50 (2)	•
BUN (MG %)		12.00 ± 1.73 (3)	15.00 ± .577 (3)		15.00 ± 1.00 (3)		14.00 ± 1.00 (2)	
CREAT (MG %)		.67 ± .033 (3)	.80 ± .058 (3)	A	.77 ± .033 (3)	A	.65 ± .050 (2)	
URIC ACID (MG)		.13 ± .033 (3)	.17 ± .033 (3)	B	.37 ± .033 (3)	* D	.35 ± .050 (2)	* D
NA (MEQ/L)		145.00 ± 1.00 (3)	146.67 ± .333 (3)		147.00 ± 1.00 (3)		144.00 ± 2.00 (2)	
K (MEQ/L)		4.60 ± .252 (3)	4.67 ± .067 (3)		5.00 ± .173 (3)		4.80 ± .100 (2)	
CO_2 (MEQ/L)		22.00 ± .577 (3)	22.33 ± 1.33 (3)		21.00 ± 1.00 (3)		22.50 ± .500 (2)	
CL (MEQ/L)		112.33 ± .882 (3)	113.33 ± 1.45 (3)		114.33 ± .333 (3)		112.00 ± 2.00 (2)	
CA (MG %)		10.00 ± .173 (3)	10.43 ± .291 (3)		10.23 ± .233 (3)		10.10 ± .200 (2)	
P (MG %)		4.03 ± .186 (3)	4.20 ± .208 (3)		4.70 ± .252 (3)		4.40 ± .200 (2)	
NA-(CL+CO_2)		10.67 ± .882 (3)	11.00 ± .577 (3)		11.67 ± .333 (3)		9.50 ± .500 (2)	
CHOL (MG %)		163.33 ± 37.4 (3)	145.00 ± 8.08 (3)		143.33 ± 14.5 (3)		196.00 ± 35.0 (2)	
TRIG (MG %)		11.67 ± 1.33 (3)	13.00 ± 2.31 (3)		23.00 ± 6.08 (3)		43.50 ± 8.50 (2)	*
BILI (MG %)		.10 ± 0.00 (3)	.10 ± 0.00 (3)		.13 ± .033 (3)	B	.20 ± 0.00 (2)	D
SGOT (MU/ML)		40.00 ± 2.08 (3)	45.00 ± 1.53 (3)		52.67 ± 4.67 (3)		42.00 ± 4.00 (2)	
SGPT (MU/ML)		45.33 ± 7.42 (3)	29.33 ± 3.18 (3)		30.67 ± 1.33 (3)		13.00 ± 1.00 (2)	* C
LDH (MU/ML)		81.00 ± 14.6 (3)	73.33 ± 14.8 (3)		116.67 ± 20.4 (3)		119.50 ± 21.5 (2)	
ALK-P (MU/ML)		128.33 ± 22.3 (3)	142.67 ± 5.78 (3)		79.67 ± 11.7 (3)		142.50 ± 51.5 (2)	
IRON (MCG %)		158.00 ± 35.5 (3)	131.00 ± 16.0 (3)		244.67 ± 22.4 (3)		251.00 ± 81.0 (2)	
PROTEIN (GM %)		5.87 ± .088 (3)	5.83 ± .120 (3)		5.80 ± .173 (3)		5.50 ± .200 (2)	
ALBUMIN (GM %)		2.83 ± .033 (3)	2.70 ± .115 (3)		3.07 ± .067 (3)		2.70 ± 0.00 (2)	
GLOBULIN (GM%)		3.03 ± .120 (3)	3.13 ± .058 (3)		2.73 ± .120 (3)		2.80 ± .200 (2)	
A/G RATIO		.94 ± .059 (3)	.87 ± .052 (3)		1.12 ± .039 (3)	A	.97 ± .070 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES.   LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 198

EFFECTS OF LAP ON CLINICAL CHEMISTRY
OF FEMALE DOGS AFTER 8 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS: 5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
GLUCOSE (MG %)		109.00 ± 1.53 (3)	94.00 ± 3.00 (3)		96.33 ± 2.19 (3)		108.00 ± 9.17 (3)	
BUN (MG %)		14.67 ± 1.45 (3)	15.00 ± .577 (3)		1[illegible].00 ± 2.08 (3)		13.00 ± 2.52 (3)	
CREAT (MG %)		.80 ± .058 (3)	.77 ± .033 (3)		.77 ± .033 (3)		.67 ± .033 (3)	A
URIC ACID (MG)		.27 ± .120 (3)	.13 ± .033 (3)	*	.30 ± 0.00 (3)	*	.40 ± .200 (3)	*
NA (MEQ/L)		147.67 ± .882 (3)	147.00 ± 1.00 (3)		145.00 ± 0.00 (3)		148.33 ± 1.45 (3)	
K (MEQ/L)		4.57 ± .088 (3)	4.23 ± .067 (3)		4.77 ± .120 (3)		4.60 ± .153 (3)	
CO_2 (MEQ/L)		21.67 ± .333 (3)	22.67 ± .333 (3)		21.67 ± .333 (3)		21.67 ± .882 (3)	
CL (MEQ/L)		113.67 ± .882 (3)	112.33 ± .882 (3)		113.00 ± 0.00 (3)		112.00 ± 1.53 (3)	
CA (MG %)		10.63 ± .033 (3)	10.[illegible]0 ± .153 (3)		10.57 ± .120 (3)		10.77 ± .273 (3)	
P (MG %)		4.70 ± .153 (3)	4.27 ± .145 (3)		3.90 ± .1[illegible]0 (3)		5.00 ± .436 (3)	
$NA-(CL+CO_2)$		12.33 ± .333 (3)	12.00 ± 1.15 (3)		11.33 ± .333 (3)		14.67 ± 1.20 (3)	
CHOL (MG %)		143.67 ± 5.78 (3)	195.00 ± 24.0 (3)		166.00 ± 17.8 (3)		205.33 ± 21.3 (3)	
TRIG (MG %)	*	24.33 ± 9.87 (3)	22.67 ± 2.40 (3)	*	24.33 ± 6.17 (3)	*	38.00 ± .577 (3)	*
BILI (MG %)		.13 ± .033 (3)	.10 ± 0.00 (3)	B	.17 ± .033 (3)	B	.27 ± .067 (3)	D
SGGT (MU/ML)		47.67 ± 4.84 (3)	43.67 ± 3.38 (3)		40.33 ± .333 (3)		35.00 ± 3.21 (3)	
SGPT (MU/ML)		35.67 ± 4.18 (3)	34.67 ± 2.60 (3)		28.33 ± 3.84 (3)		14.33 ± 1.86 (3)	* C
LDH (MU/ML)	*	79.67 ± 10.1 (3)	98.67 ± 32.5 (3)		113.67 ± 2.60 (3)	*	70.00 ± 32.0 (3)	
ALK-P (MU/ML)		83.67 ± 19.7 (3)	120.67 ± 13.2 (3)	*	107.67 ± 15.2 (3)	*	146.67 ± 68.2 (3)	*
IRON (MCG %)		183.67 ± 20.8 (3)	183.33 ± 24.7 (3)		140.00 ± 16.0 (3)		265.00 ± 19.8 (3)	
PROTEIN (GM %)	*	5.67 ± .033 (3)	6.00 ± .058 (3)	*	5.90 ± .058 (3)	*	6.33 ± .296 (3)	
ALBUMIN (GM %)		2.97 ± .033 (3)	3.00 ± .115 (3)		3.10 ± .115 (3)		3.30 ± .351 (3)	
GLOBULIN (GM%)		2.70 ± 0.00 (3)	3.00 ± .153 (3)		2.80 ± .173 (3)		3.03 ± .088 (3)	
A/G RATIO		1.31 ± .197 (3)	1.01 ± .084 (3)		1.12 ± .110 (3)		1.10 ± .142 (3)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D, RATIO TEST CANNOT BE CALCULATED - * .

TABLE 199

EFFECTS OF LAP ON CLINICAL CHEMISTRY
OF HALF DOGS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
GLUCOSE (MG %)		96.33 ± 10.0 (3)	101.00 ± 5.57 (3)		117.67 ± 2.40 (3)		103.50 ± .500 (2)	
BUN (MG %)		16.00 ± 1.00 (3)	17.67 ± 1.45 (3)		15.00 ± 0.00 (3)		15.50 ± .500 (2)	
CREAT (MG %)		.80 ± 0.00 (3)	.90 ± .058 (3)	A	.90 ± 0.00 (3)	A	.90 ± 0.00 (2)	A
URIC ACID (MG)		.43 ± .033 (3)	.50 ± .058 (3)		.43 ± .085 (3)		.50 ± .100 (2)	
NA (MEQ/L)		143.33 ± .333 (3)	145.33 ± .333 (3)		144.33 ± .333 (3)		143.00 ± 2.00 (2)	
K (MEQ/L)		5.20 ± .305 (3)	5.00 ± .058 (3)		5.10 ± .306 (3)		5.40 ± .200 (2)	
CO_2 (MEQ/L)		22.67 ± .333 (3)	23.00 ± 1.00 (3)		21.33 ± 1.45 (3)		23.50 ± .500 (2)	
CL (MEQ/L)		113.33 ± .333 (3)	115.67 ± 1.67 (3)		116.00 ± 1.00 (3)		113.00 ± 1.00 (2)	
CA (MG %)		10.00 ± .200 (3)	10.27 ± .219 (3)		9.87 ± .240 (3)		10.30 ± .400 (2)	
P (MG %)		4.47 ± .233 (3)	4.63 ± .418 (3)		4.63 ± .120 (3)		4.60 ± .200 (2)	
$NA-(CL+CO_2)$		7.33 ± .333 (3)	6.67 ± .333 (3)		7.00 ± .577 (3)		6.50 ± .500 (2)	
CHOL (MG %)		154.67 ± 34.3 (3)	153.67 ± 2.33 (3)		140.67 ± 19.7 (3)		192.00 ± 16.0 (2)	
TRIG (MG %)		50.67 ± 10.2 (3)	49.67 ± 4.91 (3)		55.67 ± 3.28 (3)		68.50 ± .500 (2)	
BILI (MG %)		.10 ± 0.00 (3)	.10 ± 0.00 (3)		.10 ± 0.00 (3)		.15 ± .050 (2)	D
SGOT (MU/ML)		39.33 ± .882 (3)	36.67 ± 2.03 (3)		36.67 ± 3.71 (3)		42.50 ± 4.50 (2)	
SGPT (MU/ML)		50.00 ± 4.51 (3)	38.00 ± 2.52 (3)		30.00 ± 2.00 (3)	* B	18.00 ± 0.00 (2)	+ C
LDH (MU/ML)		119.67 ± 4.70 (3)	64.67 ± 11.5 (3)	+ B	61.00 ± 2.08 (3)	+ B	59.50 ± .500 (2)	+ B
ALK-P (MU/ML)		113.67 ± 10.8 (3)	125.00 ± 17.0 (3)		68.00 ± 7.09 (3)		117.00 ± 24.0 (2)	
IRON (MCG %)	*	171.33 ± 1.45 (3)	217.00 ± 24.0 (3)		218.67 ± 38.0 (3)		243.50 ± 124. (2)	
PROTEIN (GM %)		5.83 ± .145 (3)	5.87 ± .186 (3)		5.47 ± .133 (3)		5.65 ± .250 (2)	
ALBUMIN (GM %)		2.67 ± .088 (3)	2.60 ± .115 (3)		2.67 ± .033 (3)		2.65 ± .150 (2)	
GLOBULIN (GM%)		3.17 ± .133 (3)	3.27 ± .088 (3)		2.80 ± .153 (3)		3.00 ± .100 (2)	
A/G RATIO		.85 ± .049 (3)	.79 ± .028 (3)		.96 ± .062 (3)	A	.88 ± .020 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 200

EFFECTS OF LAP ON CLINICAL CHEMISTRY
OF FEMALE DOGS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .5 MG/KG/DAY	T R	5.0 MG/KG/DAY	T R	50 MG/KG/DAY	T R
GLUCOSE (MG %)		105.67 ± 7.69 (3)	102.60 ± 8.33 (3)		105.67 ± 3.71 (3)		91.50 ± 3.50 (2)	
BUN (MG %)		18.67 ± 2.19 (3)	20.33 ± 1.33 (3)		17.67 ± 1.67 (3)		22.50 ± 1.50 (2)	
CREAT (MG %)		.83 ± .033 (3)	.93 ± .033 (3)	A	.93 ± .033 (3)	A	1.10 ± 0.00 (2)	+ B
URIC ACID (MG)		.53 ± .033 (3)	.43 ± .033 (3)	A	.53 ± .033 (3)		.55 ± .050 (2)	
NA (MEQ/L)		144.67 ± .333 (3)	144.33 ± 1.45 (3)		143.33 ± .882 (3)		147.50 ± .500 (2)	
K (MEQ/L)		4.70 ± .058 (3)	4.77 ± .133 (3)		5.13 ± .333 (3)		5.40 ± .200 (2)	
CO_2 (MEQ/L)		22.00 ± 0.00 (3)	20.00 ± 1.73 (3)		22.00 ± .5[illegible] (3)		21.00 ± 0.00 (2)	
CL (MEQ/L)		115.00 ± 1.15 (3)	115.67 ± 1.20 (3)		115.00 ± .577 (3)		115.00 ± 2.00 (2)	
CA (MG %)		10.30 ± .100 (3)	10.03 ± .145 (3)		10.20 ± .100 (3)		10.90 ± .300 (2)	
P (MG %)		4.43 ± .291 (3)	4.60 ± .100 (3)		3.93 ± .088 (3)		5.65 ± .250 (2)	* A
NA-(CL+CO_2)		7.67 ± 1.20 (3)	8.67 ± .882 (3)		6.33 ± 1.45 (3)		11.50 ± 2.50 (2)	
CHOL (MG %)		149.33 ± 6.89 (3)	209.00 ± 17.0 (3)	* A	153.67 ± 7.88 (3)		174.00 ± 4.00 (2)	
TRIG (MG %)		61.33 ± 2.03 (3)	122.00 ± 14.2 (3)		57.67 ± 19.9 (3)		116.00 ± 12.0 (2)	
BILI (MG %)		.10 ± 0.00 (3)	.10 ± 0.00 (3)		.17 ± .033 (3)	D	.20 ± 0.00 (2)	D
SGOT (MU/ML)		38.33 ± 2.03 (3)	34.67 ± 2.19 (3)		41.33 ± 2.91 (3)		33.50 ± .500 (2)	
SGPT (MU/ML)	*	43.67 ± .333 (3)	51.33 ± 7.97 (3)		39.00 ± 7.57 (3)		28.00 ± 10.0 (2)	
LDH (MU/ML)		73.67 ± 17.7 (3)	67.67 ± 10.3 (3)		52.33 ± 7.36 (3)		81.50 ± 13.5 (2)	
ALK-P (MU/ML)		98.67 ± 23.1 (3)	132.33 ± 7.69 (3)		124.33 ± 16.2 (3)		160.50 ± 73.5 (2)	
IRON (MCG %)		244.33 ± 21.2 (3)	235.67 ± 31.4 (3)		224.33 ± 40.2 (3)		306.50 ± 111. (2)	
PROTEIN (GM %)		5.67 ± .120 (3)	5.83 ± .133 (3)		5.57 ± .088 (3)		6.05 ± .250 (2)	
ALBUMIN (GM %)		2.80 ± .100 (3)	2.70 ± .058 (3)		2.77 ± .088 (3)		3.00 ± .200 (2)	
GLOBULIN (GM%)		2.87 ± .033 (3)	3.13 ± .186 (3)		2.80 ± .153 (3)		3.05 ± .050 (2)	
A/G RATIO		.97 ± .0[illegible] (3)	.87 ± .066 (3)		1.03 ± .085 (3)		.98 ± .050 (2)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES. LAP ADMINISTERED DAILY BY CAPSULE
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 201

EFFECTS OF LAP ON CLINICAL CHEMISTRY OF MALE DOGS
AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLES	CONTROL GROUP	TREATMENT GROUPS 0.5 MG/KG/DAY	5.0 MG/KG/DAY	50.0 MG/KG/DAY
GLUCOSE (MG %)	84	94	94	94
BUN (MG %)	19	15	15	9
CREAT (MG %)	0.6	0.7	0.8	0.7
URIC ACID (MG %)	0.4	0.2	0.3	0.4
NA (MEQ/L)	145	145	147	147
K (MEQ/L)	4.9	5.2	5.0	4.6
CO_2 (MEQ/L)	20	20	23	22
CL (MEQ/L)	113	113	113	113
CA (MG %)	9.9	10.1	10.5	10.5
P (MG %)	4.6	4.2	4.1	4.6
NA-(CL+CO_2)	12	12	11	12
CHOL (MG %)	154	187	175	133
TRIG (MG %)	12	18	23	14
BILI (MG %)	0.1	0.1	0.1	0.1
SGOT (MU/ML)	52	45	37	38
SGPT (MU/ML)	36	30	38	29
LDH (MU/ML)	168	80	62	[illegible]
ALK-P (MU/ML)	135	156	118	69
IRON (MCG %)	193	173	245	135
PROTEIN (GM %)	5.9	5.8	6.4	5.9
ALBUMIN (GM %)	2.7	2.7	3.1	3.1
GLOBULIN (GM %)	3.2	3.1	3.3	2.8
A/G RATIO	0.84	0.87	0.94	1.11

ONE DOG IN EACH GROUP
LAP WAS ADMINISTERED DAILY BY CAPSULE

TABLE 202

EFFECTS OF LAP ON CLINICAL CHEMISTRY OF FEMALE DOGS
AFTER 4 WEEKS OF TREATMENT AND 4 WEEKS OF RECOVERY

DEPENDENT VARIABLES	CONTROL GROUP	TREATMENT GROUPS 0.5 MG/KG/DAY	5.0 MG/KG/DAY	50.0 MG/KG/DAY
GLUCOSE (MG %)	106	97	89	97
BUN (MG %)	20	14	16	14
CREAT (MG %)	0.8	0.8	0.8	0.7
URIC ACID (MG %)	0.3	0.2	0.1	0.2
NA (MEQ/L)	148	147	146	148
K (MEQ/L)	4.5	4.8	4.6	5.2
CO_2 (MEQ/L)	21	21	24	25
CL (MEQ/L)	114	116	112	114
CA (MG %)	10.4	10.5	10.6	10.4
P (MG %)	4.3	4.4	4.4	5.5
NA-(CL+CO_2)	13	10	10	9
CHOL (MG %)	128	130	236	119
TRIG (MG %)	8	16	63	21
BILI (MG %)	0.1	0.1	0.1	0.1
SGOT (MU/ML)	46	[illegible]	28	32
SGPT (MU/ML)	53	33	22	20
LDH (MU/ML)	76	64	97	48
ALK-P (MU/ML)	78	139	113	65
IRON (MCG %)	165	152	282	211
PROTEIN (GM %)	5.5	5.7	5.8	5.7
ALBUMIN (GM %)	2.9	2.8	3.0	3.0
GLOBULIN (GM %)	2.6	2.9	2.8	2.7
A/G RATIO	1.12	0.97	1.07	1.11

ONE DOG IN EACH GROUP
LAP WAS ADMINISTERED DAILY BY CAPSULE

Table 2[illegible]

MICROSCOPIC LESIONS IN MALE DOGS AFTER 4 WEEKS OF LAP TREATMENT

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.5	5.0	50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Epididymis					
Aspermia				31	
Liver					
Lymphocytes - paravascular	03				
Lung					
Alveolar collapse	03			31	
Pneumonia, interstitial		13	23		
Lymph node					
Congestion	03				
Pituitary					
Cysts	03	13		31,37*	
Testes					
Inactive				31	
Thyroid					
Hyperplasia of follicular cells			23		

* Died on Day 2 of treatment.

Table 204

MICROSCOPIC LESIONS IN FEMALE DOGS AFTER 4 WEEKS OF LAP TREATMENT

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.5	5.0	50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Lung					
Alveolar collapse			24	32	
Pneumonia, interstitial	04	14			
Pituitary					
Cysts			24		
Spleen					
Pigmentation (hemosiderosis)			24		
Thyroid					
Hyperplasia of follicular cells			24		

Table 205

MICROSCOPIC LESIONS IN MALE DOGS AFTER 13 WEEKS OF LAP TREATMENT

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.5	5.0	50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Adrenals					
Vacuolation of cells of outer cortex	05	19	29		
Kidney					
Medulla-calcification	01,05,09	11,19	21,25	33,35	
Lung					
Lymphocytes - interstitial	09				
Alveolar collapse/alveolar dilation		15,19	25,29	33	
Alveolar collapse			21		
Pituitary					
Cysts		15,19	21		
Salivary gland					
Lymphocytes - interstitial				33	
Testes					
Inactive				33	

Table 206

MICROSCOPIC LESIONS IN FEMALE DOGS AFTER 13 WEEKS OF LAP TREATMENT

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.5	5.0	50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Kidney					
Congestion				36*	
Medulla - calcification	02,06,10	12,16	22,26	34	
Liver					
Congestion				36*	
Lung					
Alveolar collapse		16			
Alveolar collapse/alveolar dilation	10		22,26	34,40	
Alveolar collapse and congestion				36*	
Lymphocytes - interstitial			30		
Lymph node					
Congestion				36*	
Pituitary					
Cysts	10	12,16	26	36*	
Salivary gland					
Lymphocytes - interstitial			30		

* Died on Day 41 of treatment.

MICROSCOPIC LESIONS IN MALE DOGS AFTER 4 WEEKS OF LAP TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.5	5.0	50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Liver					
WBC parenchymal		17			
Lung					
Granuloma		17			
Alveolar collapse			27		
Lymph node					
Granuloma in capsule			27		
Pituitary					
Cysts	07		27	39	
Testes					
Atrophy				39	

Table 208

MICROSCOPIC LESIONS IN FEMALE DOGS AFTER 4 WEEKS OF LAP TREATMENT AND 4 WEEKS OF RECOVERY

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.5	5.0	50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Cholecyst					
Lymphocytes - interstitial (in submucosa)				38	
Lung					
Alveolar collapse and granuloma			28		
Pituitary					
Cysts	08				
Thymus					
Fibrosis (para and peri) and hyperplasia - vascular				38	

TABLE 209

EFFECTS OF LAP ON BODY WEIGHTS (G)
OF MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
INITIAL		139.6 ± 2.82 (20)	141.7 ± 1.93 (20)		142.4 ± 1.93 (20)		145.1 ± 1.73 (20)	
WEEK 1	*	198.2 ± 4.64 (20)	201.1 ± 2.37 (20)		188.3 ± 3.96 (20)		116.9 ± 2.47 (20)	+ C
WEEK 2		251.8 ± 4.09 (20)	249.1 ± 3.07 (20)		236.4 ± 4.32 (20)	*	130.6 ± 3.15 (20)	+ C
WEEK 3		295.8 ± 4.12 (20)	291.3 ± 3.08 (20)		282.5 ± 4.76 (20)		151.7 ± 3.27 (18)	+ C
WEEK 4	*	329.0 ± 4.27 (20)	322.1 ± 4.07 (20)		316.0 ± 6.24 (20)		165.7 ± 3.18 (18)	+ C
WEEK 5		349.2 ± 4.61 (20)	347.5 ± 4.54 (20)		338.6 ± 5.73 (20)		188.5 ± 3.78 (17)	+ C
WEEK 6		369.6 ± 4.69 (20)	365.1 ± 4.63 (20)		360.0 ± 6.42 (19)		203.7 ± 5.51 (12)	+ C
WEEK 7		394.7 ± 5.21 (20)	386.3 ± 5.10 (20)		382.6 ± 6.92 (19)		211.7 ± 5.35 (11)	+ C
WEEK 8		415.4 ± 5.54 (20)	406.4 ± 5.41 (20)		402.1 ± 7.30 (19)		233.9 ± 6.76 (10)	+ C
WEEK 9		429.7 ± 6.36 (20)	420.2 ± 6.27 (20)		419.2 ± 8.08 (19)		235.8 ± 8.15 (10)	+ C
WEEK 10		447.7 ± 6.47 (20)	435.2 ± 6.48 (20)		434.7 ± 8.48 (19)		254.7 ± 10.5 (7)	+ C
WEEK 11		460.9 ± 6.81 (20)	444.6 ± 8.72 (20)		446.9 ± 8.81 (19)		257.7 ± 12.9 (7)	+ C
WEEK 12		468.5 ± 7.61 (20)	458.5 ± 6.36 (20)		458.8 ± 8.85 (19)		260.8 ± 14.2 (6)	+ C
WEEK 13		468.2 ± 8.93 (20)	467.9 ± 6.90 (20)		468.6 ± 9.00 (19)		265.0 ± 12.0 (6)	+ C

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 210

EFFECTS OF LAP ON BODY WEIGHTS (G)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
INITIAL		130.7 ± 1.44 (20)	128.7 ± 1.54 (20)		126.1 ± 1.86 (20)		132.1 ± 1.28 (20)	
WEEK 1	+	171.2 ± 1.41 (20)	166.6 ± 2.34 (20)		147.0 ± 7.13 (20)	*	109.3 ± 1.64 (19)	+ B
WEEK 2		196.6 ± 1.93 (20)	189.5 ± 2.78 (20)		175.1 ± 2.57 (20)	+	119.9 ± 1.84 (20)	+ C
WEEK 3		215.9 ± 2.23 (20)	210.2 ± 3.71 (20)		197.2 ± 3.45 (20)	+	131.9 ± 2.59 (20)	+ C
WEEK 4		233.1 ± 2.56 (20)	224.6 ± 3.88 (20)		209.9 ± 3.47 (20)	+	142.6 ± 2.89 (20)	+ C
WEEK 5		241.9 ± 3.11 (20)	235.7 ± 4.44 (20)		225.5 ± 3.74 (20)	*	152.2 ± 3.42 (19)	+ B
WEEK 6		254.4 ± 3.38 (20)	243.2 ± 4.69 (20)		231.9 ± 4.25 (20)	+	158.5 ± 3.86 (17)	+ B
WEEK 7		265.2 ± 3.78 (20)	256.5 ± 5.29 (20)		242.2 ± 4.33 (20)	+	157.6 ± 3.62 (17)	+ C
WEEK 8		272.8 ± 3.85 (20)	266.0 ± 5.67 (20)		253.9 ± 4.56 (20)		173.1 ± 5.56 (14)	+ B
WEEK 9		280.1 ± 3.67 (20)	274.3 ± 5.80 (20)		258.5 ± 4.57 (20)	*	174.8 ± 6.10 (13)	+ B
WEEK 10		291.0 ± 4.32 (20)	279.9 ± 6.08 (20)		266.8 ± 5.22 (20)	*	181.3 ± 6.67 (12)	+ B
WEEK 11		295.5 ± 4.75 (20)	285.4 ± 5.26 (20)		270.0 ± 4.88 (20)	*	189.7 ± 6.71 (12)	+ B
WEEK 12		296.9 ± 4.27 (20)	289.6 ± 6.09 (20)		273.9 ± 5.19 (20)	*	193.4 ± 7.06 (11)	+ B
WEEK 13		296.0 ± 4.32 (20)	291.0 ± 6.52 (20)		275.7 ± 6.18 (20)		196.6 ± 7.99 (11)	+ B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 211

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHT (G)
OF MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
WEEK 1	+	58.6 ± 2.93 (20)	59.3 ± 1.03 (20)		45.9 ± 2.72 (20)	*	-28.1 ± 1.98 (20)	+ D
WEEK 2		53.6 ± 1.32 (20)	48.0 ± 1.16 (20)	*	48.2 ± 1.08 (20)	*	13.8 ± 1.50 (20)	+ D
WEEK 3		44.0 ± 1.45 (20)	42.2 ± 1.39 (20)		46.1 ± 1.44 (20)		22.2 ± 1.19 (18)	+ C
WEEK 4	+	33.2 ± 1.47 (20)	30.8 ± 1.66 (20)		33.5 ± 4.80 (20)		14.1 ± 3.08 (18)	+ C
WEEK 5	+	20.1 ± 1.63 (20)	25.4 ± 1.54 (20)	*	22.5 ± 5.67 (20)		21.9 ± 1.64 (17)	
WEEK 6	+	20.5 ± 1.30 (20)	17.7 ± 1.09 (20)		19.9 ± 2.89 (19)		14.7 ± 2.29 (12)	*
WEEK 7	+	25.0 ± 1.20 (20)	21.1 ± 1.33 (20)	*	22.6 ± 2.96 (19)		9.9 ± 2.16 (11)	+ C
WEEK 8		20.6 ± 1.20 (20)	20.0 ± 1.23 (20)		19.5 ± 1.31 (19)		24.2 ± 2.53 (10)	
WEEK 9		14.4 ± 1.25 (20)	13.9 ± 1.59 (20)		17.1 ± 1.49 (19)		1.9 ± 3.30 (10)	+ D
WEEK 10		18.0 ± 1.04 (20)	15.0 ± 1.57 (20)		15.5 ± 1.24 (19)		19.0 ± 2.02 (7)	
WEEK 11	+	13.1 ± 1.29 (20)	9.4 ± 5.38 (20)		12.3 ± .970 (19)		3.0 ± 5.08 (7)	
WEEK 12	+	7.7 ± 1.27 (20)	13.9 ± 5.36 (20)		11.8 ± 1.26 (19)	*	9.2 ± 3.43 (6)	
WEEK 13		-.3 ± 3.02 (20)	9.4 ± 2.62 (20)		9.8 ± 3.53 (19)		4.2 ± 6.18 (6)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 212

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHT (G)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	BC	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
WEEK 1	+	40.5 ± 1.43 (20)	38.0 ± 1.49 (20)		20.9 ± 7.95 (20)	*	-22.5 ± 1.33 (19)	+ D
WEEK 2	+	25.4 ± 1.09 (20)	22.9 ± 1.35 (20)		28.1 ± 7.89 (20)		10.3 ± .773 (19)	+ D
WEEK 3		19.2 ± 1.25 (20)	20.7 ± 1.38 (20)		22.1 ± 1.29 (20)		12.1 ± 1.33 (20)	+ B
WEEK 4		17.2 ± 1.02 (20)	14.4 ± 1.48 (20)		12.7 ± .807 (20)		10.6 ± 1.00 (20)	+ B
WEEK 5		8.9 ± .966 (20)	11.1 ± 1.32 (20)		15.6 ± 1.16 (20)	+ B	9.8 ± 1.11 (19)	
WEEK 6		12.4 ± 1.19 (20)	7.4 ± .899 (20)	* B	6.3 ± 1.09 (20)	+ B	8.2 ± .754 (17)	A
WEEK 7		10.9 ± 1.27 (20)	13.2 ± 1.27 (20)		10.4 ± .831 (20)		-.9 ± .913 (17)	+ D
WEEK 8	*	7.6 ± 1.34 (20)	9.6 ± 1.41 (20)		11.6 ± .755 (20)	*	14.9 ± 1.70 (14)	*
WEEK 9	*	7.3 ± 1.48 (20)	8.3 ± .861 (20)		4.6 ± .626 (20)		.1 ± 1.07 (13)	+ D
WEEK 10		10.9 ± 1.53 (20)	5.6 ± 1.18 (20)	B	8.4 ± 1.22 (20)		5.6 ± 1.93 (12)	A
WEEK 11		4.5 ± 1.24 (20)	5.6 ± 1.19 (20)		3.2 ± 1.11 (20)		8.5 ± 1.32 (12)	
WEEK 12	*	1.4 ± 1.76 (20)	4.3 ± 1.20 (20)	•	4.0 ± .872 (20)	•	3.1 ± .977 (11)	•
WEEK 13		-.9 ± 2.14 (20)	1.3 ± 2.21 (20)	•	1.8 ± 2.01 (20)	•	3.3 ± 1.57 (11)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 213

EFFECTS OF LAP ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS		
		.005 %	0.05 %	0.5 %
WEEK 1	18.18	19.37	16.81	4.59
WEEK 2	23.69	23.13	21.51	9.76
WEEK 3	26.60	24.30	23.28	10.25
WEEK 4	25.81	24.51	23.09	12.65
WEEK 5	25.81	24.63	23.99	11.96
WEEK 6	26.02	25.22	24.15	13.06
WEEK 7	24.08	24.83	23.71	13.23
WEEK 8	27.79	23.91	23.50	14.26
WEEK 9	25.86	24.61	23.97	12.76
WEEK 10	25.92	24.70	24.01	15.70
WEEK 11	25.64	25.71	24.68	15.73
WEEK 12	22.58	24.78	23.74	14.63
WEEK 13	24.11	24.81	25.30	17.89

ENTRIES ARE MEANS. GROUP N SAME AS IN BODY WEIGHT TABLES.

TABLE 214

EFFECTS OF LAP ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .005 %	0.05 %	0.5 %
WEEK 1	16.82	16.46	13.90	3.97
WEEK 2	18.73	18.11	16.02	8.56
WEEK 3	22.20	17.98	16.53	9.64
WEEK 4	19.49	17.76	16.44	10.41
WEEK 5	21.49	18.25	16.72	10.39
WEEK 6	21.17	18.59	17.27	10.49
WEEK 7	18.14	17.99	16.94	9.70
WEEK 8	24.44	17.44	18.14	10.37
WEEK 9	22.52	18.24	16.71	10.77
WEEK 10	23.93	17.44	15.96	11.65
WEEK 11	24.26	18.42	17.20	15.52
WEEK 12	19.62	16.73	16.54	11.15
WEEK 13	20.36	17.28	16.76	12.05

ENTRIES ARE MEANS. GROUP N SAME AS IN BODY WEIGHT TABLES.

TABLE 215

EFFECTS OF LAP ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	W	.05 % IN DIET	W	.50 % IN DIET	W
WEEK 1	91.8 ± 3.64 (8)	96.4 ± 1.17 (8)		89.3 ± .901 (8)		38.9 ± 2.57 (8)	*
WEEK 2	94.2 ± 1.77 (8)	92.8 ± .913 (8)		91.1 ± 1.52 (8)		74.7 ± 1.10 (8)	*
WEEK 3	90.0 ± 1.80 (8)	83.4 ± 2.88 (8)		82.4 ± 1.09 (8)		67.6 ± 5.21 (8)	*
WEEK 4	78.4 ± 1.74 (8)	75.1 ± .624 (8)		73.1 ± 1.16 (8)		76.3 ± 4.95 (8)	
WEEK 5	73.9 ± 1.08 (8)	70.9 ± .792 (8)		70.9 ± 1.46 (8)		63.3 ± 5.95 (8)	
WEEK 6	70.5 ± 1.49 (8)	69.0 ± .790 (8)		66.7 ± .778 (8)		64.0 ± 2.98 (8)	
WEEK 7	61.0 ± .850 (8)	64.3 ± .473 (8)		62.0 ± 2.26 (8)		62.4 ± 1.19 (7)	
WEEK 8	66.8 ± 2.84 (8)	58.9 ± 2.68 (8)	*	58.5 ± .523 (8)		60.0 ± .945 (7)	
WEEK 9	60.2 ± 1.91 (8)	58.4 ± 1.93 (8)		57.2 ± 1.01 (8)		53.3 ± 6.10 (7)	
WEEK 10	57.9 ± 2.26 (8)	56.7 ± .866 (8)		55.2 ± .806 (8)		52.0 ± 8.96 (7)	
WEEK 11	55.6 ± 1.79 (8)	57.8 ± 2.72 (8)		55.2 ± .771 (8)		61.5 ± 4.21 (3)	
WEEK 12	55.5 ± 1.76 (8)	54.1 ± .816 (8)		51.8 ± .743 (8)		55.7 ± 1.06 (5)	
WEEK 13	55.1 ± 1.70 (6)	54.9 ± 1.19 (8)		56.1 ± 1.53 (8)		68.1 ± 5.75 (5)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 216

EFFECTS OF LAP ON FOOD CONSUMPTION (G/KG (BODY WT)/ DAY)
OF FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	W	.05 % IN DIET	W	.50 % IN DIET	W
WEEK 1	98.2 ± 1.42 (8)	98.7 ± 1.05 (8)		96.1 ± 5.63 (8)		36.2 ± 1.95 (8)	*
WEEK 2	95.2 ± 1.04 (8)	95.6 ± 1.07 (8)		91.5 ± 1.08 (8)		71.5 ± 3.61 (8)	*
WEEK 3	1[illegible]2.3 ± 8.12 (8)	85.5 ± 1.48 (8)	*	83.8 ± .536 (8)	*	73.0 ± 1.49 (9)	*
WEEK 4	83.6 ± 1.81 (8)	79.1 ± 1.91 (8)		63.4 ± 9.46 (8)		73.0 ± 1.03 (8)	
WEEK 5	88.4 ± 6.98 (8)	77.4 ± 1.13 (8)		74.1 ± .959 (8)		68.2 ± 1.22 (8)	*
WEEK 6	82.7 ± 5.61 (8)	76.4 ± 1.40 (8)		74.5 ± .537 (8)		64.8 ± 1.35 (8)	*
WEEK 7	68.3 ± .821 (8)	70.2 ± 1.17 (8)		70.0 ± .856 (8)		61.6 ± 1.26 (8)	*
WEEK 8	88.9 ± 6.27 (8)	65.6 ± 1.05 (8)		71.9 ± 7.85 (8)		53.5 ± 5.89 (8)	*
WEEK 9	80.1 ± 5.90 (8)	66.5 ± 2.27 (8)	*	64.0 ± .958 (7)	*	60.9 ± .913 (7)	*
WEEK 10	81.8 ± 6.97 (8)	62.3 ± 1.44 (8)	*	59.8 ± 1.19 (8)	*	64.4 ± 4.04 (7)	*
WEEK 11	82.4 ± 6.83 (8)	64.6 ± 1.98 (8)		63.8 ± 1.53 (8)		81.4 ± 9.16 (7)	
WEEK 12	65.8 ± 4.71 (8)	57.8 ± 1.08 (8)		60.4 ± 1.32 (8)		53.7 ± 6.37 (7)	
WEEK 13	71.5 ± 2.77 (8)	61.5 ± 1.22 (8)	*	62.9 ± 2.17 (8)	*	63.7 ± 2.25 (6)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 217

DOSES OF LAP (MG/KG (BODY WT)/DAY) IN DIETS CONSUMED BY MALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS .005 % IN DIET	.05 % IN DIET	.50 % IN DIET
WEEK 1	4.82	44.6	194.6
WEEK 2	4.64	45.5	373.5
WEEK 3	4.17	41.2	338.0
WEEK 4	3.81	36.6	381.5
WEEK 5	3.54	35.5	316.3
WEEK 6	3.45	33.3	320.2
WEEK 7	3.21	31.0	312.1
WEEK 8	2.94	29.2	300.2
WEEK 9	2.92	28.6	266.6
WEEK 10	2.84	27.6	260.0
WEEK 11	2.89	27.6	307.6
WEEK 12	2.70	25.9	278.3
WEEK 13	2.74	28.0	340.4

TABLE 218

DOSES OF LAP (MG/KG (BODY WT)/DAY) IN DIETS CONSUMED BY FEMALE RATS DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS .005 % IN DIET	.05 % IN DIET	.50 % IN DIET
WEEK 1	4.94	48.1	18[illegible].0
WEEK 2	4.78	45.8	357.3
WEEK 3	4.28	41.9	363.2
WEEK 4	3.95	31.7	365.0
WEEK 5	3.87	37.1	341.1
WEEK 6	3.82	37.3	324.0
WEEK 7	3.51	35.0	307.9
WEEK 8	3.28	36.0	267.5
WEEK 9	3.33	32.0	304.6
WEEK 10	3.12	29.9	322.2
WEEK 11	3.23	31.9	407.0
WEEK 12	2.89	30.2	268.7
WEEK 13	3.07	31.5	318.4

TABLE 219

EFFECTS OF LAP ON ORGAN WEIGHTS (G)
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
FINAL WEIGHT (G)		470.11 ± 9.19 (19)	467.90 ± 6.90 (20)		468.58 ± 9.00 (19)		271.20 ± 12.5 (5)	+ C
BRAIN		2.33 ± .045 (20)	2.27 ± .054 (20)		2.35 ± .039 (19)		2.06 ± .040 (5)	
HEART		1.81 ± .055 (20)	1.77 ± .094 (20)		1.80 ± .072 (19)		.96 ± .087 (5)	+ B
KIDNEYS		3.64 ± .096 (20)	3.51 ± .087 (20)		3.74 ± .125 (19)		2.34 ± .136 (5)	+ B
LIVER	*	13.77 ± .600 (20)	13.00 ± .289 (20)		14.32 ± .484 (19)		12.08 ± .822 (5)	
SPLEEN		.75 ± .028 (20)	.82 ± .032 (20)		.82 ± .032 (19)		1.20 ± .110 (5)	+ C
TESTES	+	3.30 ± .085 (20)	3.22 ± .075 (20)		3.37 ± .060 (18)		1.74 ± .437 (5)	* A
BRAIN/BODY		5.01 ± .107 (19)	4.84 ± .096 (20)		5.05 ± .112 (19)		7.65 ± .321 (5)	+ C
HEART/BODY		3.90 ± .135 (19)	3.79 ± .189 (20)		3.85 ± .142 (19)		3.53 ± .203 (5)	
KIDNEY/BODY		7.81 ± .194 (19)	7.50 ± .139 (20)		7.95 ± .171 (19)		8.61 ± .241 (5)	
LIVER/BODY	*	29.32 ± .948 (19)	27.77 ± .447 (20)		30.53 ± .780 (19)		44.44 ± 1.67 (5)	+ B
SPLEEN/BODY	*	1.57 ± .047 (19)	1.75 ± .058 (20)	*	1.74 ± .055 (19)	*	4.42 ± .303 (5)	+ D
TESTES/BODY	+	6.98 ± .170 (19)	6.89 ± .149 (20)		7.16 ± .133 (18)		6.38 ± 1.54 (5)	
HEART/BRAIN	*	.78 ± .024 (20)	.79 ± .041 (20)		.76 ± .024 (19)		.46 ± .033 (5)	+ B
KIDNEY/BRAIN		1.56 ± .036 (20)	1.56 ± .052 (20)		1.59 ± .044 (19)		1.14 ± .062 (5)	+ A
LIVER/BRAIN		5.88 ± .203 (20)	5.76 ± .119 (20)		6.09 ± .179 (19)		5.86 ± .384 (5)	
SPLEEN/BRAIN		.32 ± .011 (20)	.36 ± .012 (20)	A	.35 ± .013 (19)		.58 ± .045 (5)	+ D
TESTES/BRAIN	+	1.42 ± .037 (20)	1.43 ± .037 (20)		1.44 ± .029 (18)		.85 ± .224 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 220

EFFECTS OF LAP ON ORGAN WEIGHTS (G)
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
FINAL WEIGHT (G)		295.95 ± 6.32 (20)	290.95 ± 6.52 (20)		275.70 ± 6.18 (20)		196.64 ± 7.99 (11)	+ B
BRAIN		2.15 ± .028 (20)	2.20 ± .031 (20)		2.19 ± .040 (20)		2.10 ± .040 (11)	
HEART		1.20 ± .050 (20)	1.16 ± .037 (20)		1.08 ± .038 (20)		.85 ± .041 (11)	+ A
KIDNEYS		2.13 ± .054 (20)	2.16 ± .044 (20)		2.13 ± .065 (20)		1.66 ± .065 (11)	+ A
LIVER		8.33 ± .284 (20)	7.60 ± .237 (20)		7.67 ± .194 (20)		9.26 ± .262 (11)	
SPLEEN	+	.61 ± .021 (20)	.61 ± .022 (20)		.65 ± .037 (20)		1.19 ± .086 (11)	+ D
BRAIN/BODY	+	7.30 ± .144 (20)	7.62 ± .166 (20)		7.99 ± .207 (20)	*	10.88 ± .550 (11)	+ B
HEART/BODY		4.04 ± .154 (20)	3.99 ± .113 (20)		3.92 ± .140 (20)		4.33 ± .203 (11)	
KIDNEY/BODY		7.20 ± .163 (20)	7.46 ± .149 (20)		7.71 ± .182 (20)		8.51 ± .283 (11)	+
LIVER/BODY	*	28.21 ± .990 (20)	26.16 ± .641 (20)		27.88 ± .566 (20)		47.58 ± 1.53 (11)	+ D
SPLEEN/BODY	+	2.08 ± .072 (20)	2.10 ± .066 (20)		2.35 ± .112 (20)		6.14 ± .454 (11)	+ D
HEART/BRAIN		.56 ± .022 (20)	.53 ± .015 (20)		.49 ± .016 (20)	A	.40 ± .022 (11)	+ B
KIDNEY/BRAIN		.99 ± .025 (20)	.98 ± .017 (20)		.98 ± .032 (20)		.79 ± .031 (11)	+ A
LIVER/BRAIN		3.88 ± .127 (20)	3.46 ± .096 (20)		3.52 ± .088 (20)		4.43 ± .169 (11)	*
SPLEEN/BRAIN	+	.29 ± .010 (20)	.28 ± .009 (20)		.30 ± .018 (20)		.57 ± .046 (11)	+ D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 221

EFFECTS OF LAP ON HEMATOLOGY
OF MALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.065 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
			TREATMENT GROUPS					
RBC (X 106)		7.56 ± .114 (19)	7.93 ± .155 (20)		7.26 ± .108 (16)		6.37 ± .205 (5)	
HGB (G %)		15.65 ± .182 (19)	15.75 ± .181 (20)		15.04 ± .252 (16)		12.94 ± .201 (5)	+ A
HCT (%)	*	39.47 ± .550 (19)	41.57 ± 1.23 (20)		37.25 ± .691 (16)	*	36.20 ± 1.09 (5)	*
MCV (U)3		52.16 ± .336 (19)	53.10 ± .239 (20)		52.75 ± .323 (16)		58.00 ± .316 (5)	
MCH (UUG)		20.66 ± .291 (19)	20.12 ± .411 (20)		20.69 ± .225 (16)		20.50 ± .674 (5)	
MCHC (%)	*	39.58 ± .592 (19)	38.52 ± .977 (20)		40.26 ± .467 (16)		36.18 ± 1.26 (5)	*
WBC (X 103)		9.24 ± .670 (19)	11.76 ± .715 (20)		12.18 ± .802 (16)		10.51 ± .716 (5)	
PMN (%)		13.74 ± 1.24 (19)	11.85 ± 1.18 (20)		10.94 ± .819 (16)		10.80 ± 1.39 (5)	
BANDS (%)		.16 ± .086 (19)	.15 ± .082 (20)	*	.13 ± .035 (16)	*	0.00 ± 0.00 (5)	*
LYMPH (%)		80.68 ± 1.32 (19)	82.20 ± 1.23 (20)		83.50 ± 1.01 (16)		84.80 ± 1.32 (5)	
MONO (%)		4.26 ± .284 (19)	4.80 ± .313 (20)		4.63 ± .417 (16)		4.20 ± .490 (5)	
EOSIN (%)		.68 ± .217 (19)	.60 ± .197 (20)		.81 ± .245 (16)		.20 ± .200 (5)	
BASO (%)		0.00 ± 0.00 (19)	0.00 ± 0.00 (20)		0.00 ± 0.00 (16)		0.00 ± 0.00 (6)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 222

EFFECTS OF LAP ON HEMATOLOGY
OF FEMALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
RBC (X 10^6)		7.35 ± .133 (18)	7.20 ± .087 (16)		6.79 ± .128 (18)	*	5.48 ± .168 (8)	
HGB (G %)		15.30 ± .178 (18)	15.37 ± .129 (16)		14.89 ± .179 (18)		12.50 ± .232 (8)	+ A
HCT (%)		39.23 ± .815 (18)	37.76 ± .539 (16)		35.81 ± .308 (18)	*	32.40 ± 1.05 (8)	+ A
MCV $(U)^3$	*	54.22 ± .329 (18)	54.06 ± .295 (16)		53.89 ± .378 (18)		60.50 ± 1.09 (8)	
MCH (UUG)	*	20.93 ± .415 (18)	21.58 ± .208 (16)		22.10 ± .401 (18)		23.05 ± .487 (8)	*
MCHC (%)	*	39.40 ± .821 (18)	40.97 ± .405 (16)		42.68 ± 1.10 (18)	*	38.99 ± 1.10 (8)	
WBC (X 10^3)		5.46 ± .477 (18)	8.29 ± 1.04 (16)		8.75 ± .789 (18)	*	11.74 ± 1.01 (8)	
PMN (%)	+	13.72 ± 1.86 (18)	10.94 ± .766 (16)		8.44 ± .706 (18)	* A	10.63 ± 1.13 (8)	
BANDS (%)		.06 ± .056 (18)	.06 ± .063 (16)	•	0.00 ± 0.00 (18)	•	.13 ± .125 (8)	•
LYMPH (%)	+	80.56 ± 1.83 (18)	77.62 ± 4.61 (16)		86.00 ± .875 (18)	*	84.00 ± 1.24 (8)	
MONO (%)		4.61 ± .372 (18)	5.00 ± .274 (16)		4.17 ± .246 (18)		4.75 ± .366 (8)	
EOSIN (%)	*	1.06 ± .375 (18)	1.38 ± .287 (16)		1.33 ± .420 (18)		.50 ± .189 (8)	
BASO (%)		0.00 ± 0.00 (18)	0.00 ± 0.00 (16)	•	.05 ± .050 (18)	•	0.00 ± 0.00 (8)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 223

EFFECTS OF LAP ON CLINICAL CHEMISTRY
OF MALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
GLUCOSE (MG %)		134.11 ± 3.95 (19)	134.63 ± 4.50 (19)		134.63 ± 5.05 (19)		125.40 ± 5.56 (5)	
BUN (MG %)		18.26 ± 1.12 (19)	17.68 ± .753 (19)		17.63 ± .947 (19)		22.20 ± 2.46 (5)	
CREAT (MG %)	+	.62 ± .033 (17)	.66 ± .051 (16)		.48 ± .016 (17)	+ A	.56 ± .087 (5)	
URIC ACID (MG)		1.91 ± .352 (19)	2.09 ± .409 (19)		1.90 ± .340 (19)		2.12 ± .284 (5)	
NA (MEQ/L)	*	144.47 ± .589 (17)	143.31 ± .688 (16)		143.12 ± .270 (17)	*	142.60 ± 1.21 (5)	
K (MEQ/L)		4.94 ± .094 (17)	5.12 ± .088 (16)		5.50 ± .086 (17)	+	5.32 ± .334 (5)	
CO_2 (MEQ/L)		21.82 ± .530 (17)	22.00 ± .570 (16)		22.94 ± .449 (17)		21.20 ± .490 (5)	
CL (MEQ/L)		102.24 ± .838 (17)	101.56 ± 1.07 (16)		100.12 ± .674 (17)		103.80 ± 1.39 (5)	
CA (MG %)		8.81 ± .136 (17)	8.22 ± .207 (16)		8.53 ± .123 (17)		8.84 ± .150 (5)	
P (MG %)		5.65 ± .159 (17)	6.19 ± .140 (16)		6.31 ± .137 (16)	*	6.58 ± .231 (5)	*
NA-(CL+CO_2)		20.41 ± .957 (17)	19.75 ± .854 (16)		20.06 ± .774 (17)		17.60 ± 1.50 (5)	
CHOL (MG %)	+	56.12 ± 10.6 (17)	42.56 ± 1.91 (16)		54.24 ± 3.10 (17)		78.40 ± 6.56 (5)	
TRIG (MG %)	*	54.35 ± 8.74 (17)	48.19 ± 5.63 (16)		47.00 ± 4.21 (17)		17.00 ± 3.67 (5)	+ D
BILI (MG %)	*	.12 ± .013 (17)	.11 ± .006 (16)		.09 ± .006 (17)		.16 ± .024 (5)	
SGOT (MU/ML)	*	109.00 ± 9.63 (19)	121.37 ± 4.54 (19)		106.79 ± 5.20 (19)		90.60 ± 8.95 (5)	
SGPT (MU/ML)		39.11 ± 2.70 (19)	40.84 ± 2.55 (19)		32.84 ± 2.81 (19)		36.40 ± 3.98 (5)	
LDH (MU/ML)	+	1001.71 ± 129. (14)	1222.69 ± 75.1 (16)		1424.94 ± 202. (18)		1386.60 ± 411. (5)	
ALK-P (MU/ML)	*	188.26 ± 25.0 (19)	143.84 ± 11.1 (19)		145.58 ± 13.5 (19)		170.00 ± 40.3 (5)	
IRON (MCG %)		193.24 ± 14.0 (17)	183.44 ± 13.4 (16)		149.29 ± 9.32 (17)		167.00 ± 11.2 (5)	
PROTEIN (GM %)		6.19 ± .078 (17)	6.17 ± .078 (16)		6.26 ± .079 (17)		6.50 ± .123 (5)	
ALBUMIN (GM %)	+	3.08 ± .093 (17)	3.00 ± .032 (16)		2.93 ± .031 (17)		3.06 ± .081 (5)	
GLOBULIN (GM%)		3.12 ± .072 (17)	3.17 ± .055 (16)		3.34 ± .059 (17)		3.44 ± .121 (5)	
A/G RATIO	+	1.01 ± .034 (17)	.95 ± .013 (16)		.88 ± .014 (17)		.90 ± .049 (5)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE [illegible]

EFFECTS OF LAP ON CLINICAL CHEMISTRY
OF FEMALE RATS AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.005 % IN DIET	T R	.05 % IN DIET	T R	.50 % IN DIET	T R
			TREATMENT GROUPS					
GLUCOSE (MG %)		139.33 ± 5.81 (18)	139.35 ± 4.77 (20)		121.85 ± 4.27 (20)		107.00 ± 6.72 (9)	+ A
BUN (MG %)		[illegible] ± 1.01 (18)	.20 ± .770 (20)		17.50 ± .738 (20)		23.00 ± 1.79 (9)	+ A
CREAT (MG %)		[illegible] ± .028 (16)	.56 ± .023 (17)		.63 ± .034 (20)		.48 ± .040 (9)	
URIC ACID (MG)	+	1.54 ± .210 (18)	1.53 ± .265 (20)		1.55 ± .087 (20)		2.26 ± .344 (9)	
NA (MEQ/L)		141.50 ± .592 (16)	141.31 ± .637 (16)		142.55 ± .387 (20)		140.83 ± .477 (6)	
K (MEQ/L)		4.78 ± .140 (16)	4.90 ± .121 (16)		5.53 ± .120 (20)	+	5.30 ± .207 (6)	
CO_2 (MEQ/L)		19.94 ± .692 (16)	20.25 ± .443 (16)		20.35 ± .514 (20)		21.50 ± .806 (6)	
CL (MEQ/L)		103.94 ± .929 (16)	100.56 ± 1.10 (16)		103.05 ± .727 (20)		100.83 ± .703 (6)	
CA (MG %)	+	9.24 ± .102 (16)	9.15 ± .208 (17)		9.21 ± .124 (20)		10.11 ± .545 (9)	
P (MG %)	+	4.78 ± .209 (16)	5.89 ± .125 (17)	+ A	6.25 ± .198 (20)	+ A	7.67 ± .620 (9)	+ B
NA-(CL+CO_2)		17.62 ± .785 (16)	20.50 ± .935 (16)		19.15 ± .689 (20)		18.50 ± .428 (6)	
CHOL (MG %)	+	66.75 ± 3.23 (16)	64.12 ± 3.11 (17)		87.70 ± 2.87 (20)	+ A	146.67 ± 14.1 (9)	+ D
TRIG (MG %)		23.50 ± 3.40 (16)	28.71 ± 3.83 (17)		20.60 ± 3.02 (20)		28.22 ± 5.30 (9)	
BILI (MG %)	+	.11 ± .009 (16)	.12 ± .014 (16)		.15 ± .012 (18)	*	.41 ± .107 (9)	* B
SGOT (MU/ML)		88.78 ± 4.56 (18)	93.05 ± 5.12 (20)		91.90 ± 4.18 (20)		86.11 ± 6.13 (9)	
SGPT (MU/ML)		32.44 ± 1.88 (18)	27.60 ± 1.68 (20)		33.00 ± 2.46 (20)		27.78 ± 2.64 (9)	
LDH (MU/ML)		848.12 ± 117. (17)	770.89 ± 118. (18)		1215.26 ± 96.3 (19)		758.22 ± 99.7 (9)	
ALK-P (MU/ML)	*	128.33 ± 16.9 (18)	88. 0 ± 6.88 (20)	*	100.15 ± 11.3 (20)		133.67 ± 22.8 (9)	
IRON (MCG %)	*	341.19 ± 15.9 (16)	323.37 ± 15.6 (16)		297.15 ± 22.4 (20)		189.67 ± 12.5 (6)	+ B
PROTEIN (GM %)	+	6.28 ± .094 (16)	6.54 ± .145 (17)		9.61 ± 3.08 (20)		7.40 ± .520 (9)	
ALBUMIN (GM %)	+	3.14 ± .063 (16)	3.32 ± .121 (17)		4.41 ± 1.29 (20)		3.79 ± .385 (9)	
GLOBULIN (GM%)	+	3.13 ± .042 (16)	3.22 ± .049 (17)		3.63 ± .235 (20)		3.61 ± .143 (9)	*
A/G RATIO	*	1.01 ± .015 (16)	1.03 ± .012 (17)		.92 ± .016 (20)	+	1.00 ± .052 (9)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENC. INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

MICROSCOPIC LESIONS IN MALE RATS AFTER 13 WEEKS OF LAF TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.50	
	Group Designation				
	B0	B1	B2	B3*	
	Animal Number				
Adrenal					
Vacuolated cells - midcortex	103,105		146,147	173	
			149,159		
Colon					
Parasitism	118		144,148		
Heart					
Fibrosis	113				
Kidney					
Regeneration	101,113		141,143		
			147,149		
			153,155,160		
Lymphocytes - interstitial				179	
Regeneration & Lymphocytes - paravascular			150		
Liver					
Lymphocytes - parenchymal				179	
Lung					
Respiratory disease - chronic	101		144,147,154		
			157,160		
Alveolar collapse, respiratory disease - chronic	107,110,111		142,145	173	
Alveolar collapse, alveolar dilation, respiratory disease - chronic	102,103,114		153,155,158	164	
	115,116,117		159,141,143		
	120		148,149,151		
Alveolar histiocytosis, alveolar collapse, alveolar dilation, respiratory disease - chronic	105,108,109		146,156		
Alveolar collapse, alveolar histiocytosis, respiratory disease - chronic	106,112				

* Nos. 169 and 176 died during weeks 7 and 8, respectively.

Organ/Lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Alveolar histiocytosis, respiratory disease - chronic	119			161	
Alveolar collapse, hemorrhage, respiratory disease - chronic				172	
Alveolar collapse, alveolar dilation, respiratory disease - chronic, hemorrhage	104				
Respiratory disease - chronic, congestion	118		150	176	
Alveolar dilation, congestion, respiratory disease - chronic	113				
Congestion, edema, respiratory disease-chronic				169	
Lymph node					
Hemorrhage			155		
Pancreas					
Lymphocytes - interstitial			153		
Pituitary					
Cysts			154		
Prostate					
Lymphocytes - interstitial	104,106,107 108,109,110 115,119		142,145,153 154,155		
Spleen					
Pigmentation (hemosiderosis)	102,110,115	121,125,130 133,138	146,147,149 150,156,157	161,164,169 172,173,176 179	
Testes					
Atrophy	109			161,172	

Organ/Lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Atrophy, hyperplasia, interstitial cell				169,176	
Inactive (not otherwise specified)				173	
Thymus					
Hyperplasia				169,176	
Trachea					
Chronic inflammation	110,113		141,143,144	169	
			150,154,155		

Table 226

MICROSCOPIC LESIONS IN FEMALE RATS AFTER 13 WEEKS OF LAP TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.50	
	Group Designation				
	B0	B1	B2	B3 *	
	Animal Number				
Adrenal					
Vacuolated Cells - midcortex				272	
Colon					
Parasitism	204,209		258	269,270	
				274,266	
Eye					
Atrophy	215				
Heart					
Lymphocytes - interstitial			257		
Ileum					
Hyperplasia of Peyers Patches	216				
Kidney					
Chronic inflammation	215				
Lymphocytes - interstitial			254,258		
Liver					
Lymphocytes - paravascular			256		
Lymphocytes - parenchymal				278	
Lung					
Respiratory disease - chronic	201,209,215		241,245,254	261,263	
Alveolar collapse , respiratory disease -			243,244,255		
chronic			257,260		
Alveolar collapse, alveolar dilation,	202,203,204		242,246,249	262,269,271	
respiratory disease - chronic	205,206		250,253	272,274	
	207,210,211		256,259	276,278	
	212,213,214				
	217,218,220				

* Nos. 266 and 280 died during week 6

Table 226 (continued)

Organ/Lesion	Dose Level (% in Feed)				
	0	.005	.05	.50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Lung (continued)					
Alveolar histiocytosis, respiratory disease chronic				270	
Alveolar collapse, alveolar histiocytosis, respiratory disease - chronic				279	
Alveolar histiocytosis, alveolar collapse, alveolar dilation, respiratory disease - chronic	208		251		
Hemorrhage, respiratory disease - chronic			248		
Alveolar collapse, hemorrhage, respiratory disease - chronic			247,252		
Alveolar collapse, alveolar dilation, hemorrhage, respiratory disease - chronic	216,219		258		
Congestion, edema, respiratory disease - chronic			266,280		
Lymph node					
Hemorrhage			245,251,253		
Pituitary					
Cysts			253,257,259	279	
Spleen					
Pigmentation - hemosiderosis	201,202,203	221,222,223	241,242,243	261,262,263	
	204,205,206	224,225,226	244,245,246	269,266,270	
	207,208,209	227,228,229	248,249,250	271,272,274	
	210,211,212	230,231,232	252,253,254	276,278,279	
	213,215,217	234,235,236	255,256,257		
		237,238,239	258,260		
		240			

Table 226 (Concluded)

Organ/Lesion	Dose Level (% in Feed)				
	0	.005	.05	.50	
	Group Designation				
	B0	B1	B2	B3	
	Animal Number				
Thymus					
Hyperplasia				280	
Trachea					
Chronic inflammation	205		250,252,257	266	
Uterus					
Ectasia - dilated	204,205,211		241,243,246		
	220		247,253,254		
Abcess in unknown location	220				
Hypoplasia				261,262,263	
				266,269,270	
				271,272,274	
				276,278,279	
				280	

TABLE 227

EFFECTS OF LAP ON BODY WEIGHTS (G)
OF MALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.005 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R	.50 % IN DIET	T R
			TREATMENT GROUPS							
INITIAL		22.0 ± .582 (20)	22.5 ± .559 (20)		21.5 ± .727 (20)		21.1 ± .930 (20)		19.2 ± .560 (20)	
WEEK 1		22.5 ± .671 (20)	25.2 ± .614 (20)		21.0 ± .835 (20)		18.0 ± .703 (20)	+ A	15.9 ± .584 (20)	+ B
WEEK 2		24.1 ± .757 (19)	27.2 ± .668 (20)		23.0 ± .930 (20)		18.2 ± .710 (20)	+ A	15.9 ± .675 (14)	+ B
WEEK 3		22.8 ± 1.06 (18)	28.5 ± .701 (20)	+ A	24.5 ± .896 (20)		19.9 ± .927 (20)		18.1 ± .828 (13)	*
WEEK 4		28.9 ± 1.02 (17)	30.6 ± .739 (19)		26.0 ± .883 (20)		20.2 ± 1.14 (20)	+ B	20.8 ± 1.08 (12)	+ A
WEEK 5		30.4 ± .974 (17)	32.1 ± .644 (19)		27.3 ± .898 (20)		21.7 ± 1.07 (20)	+ B	21.7 ± 1.08 (12)	+ A
WEEK 6		31.2 ± 1.05 (17)	32.9 ± .675 (19)		28.0 ± .835 (20)		22.0 ± 1.17 (20)	+ B	22.7 ± 1.05 (12)	+ A
WEEK 7		32.2 ± 1.18 (17)	35.8 ± .796 (19)		30.5 ± .860 (20)		24.5 ± 1.20 (20)	+ A	26.2 ± 1.19 (12)	*
WEEK 8		33.9 ± 1.08 (17)	34.5 ± .825 (19)		30.2 ± .838 (20)		24.2 ± 1.11 (20)	+ B	26.3 ± 1.10 (12)	+ A
WEEK 9		34.5 ± 1.15 (17)	37.3 ± .764 (19)		32.2 ± .829 (20)		25.9 ± 1.16 (20)	+ A	27.4 ± 1.02 (12)	+ A
WEEK 10		35.0 ± 1.12 (17)	37.6 ± .690 (19)		32.7 ± .859 (20)		27.4 ± 1.23 (20)	+ A	28.2 ± 1.12 (12)	+ A
WEEK 11		35.9 ± 1.15 (17)	36.8 ± .694 (19)		32.0 ± .905 (20)		27.0 ± 1.05 (20)	+ A	27.9 ± .892 (12)	+ A
WEEK 12		36.3 ± 1.09 (17)	38.6 ± .739 (19)		33.1 ± 1.32 (20)		29.5 ± 1.15 (20)	+ A	29.6 ± .925 (12)	+
WEEK 13		37.1 ± 1.14 (17)	38.4 ± .589 (19)		35.1 ± .900 (20)		29.7 ± 1.10 (20)	+ A	31.0 ± .992 (12)	+

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 228

EFFECTS OF LAP ON BODY WEIGHTS (G)
OF FEMALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R	.50 % IN DIET	T R
INITIAL		19.6 ± .621 (20)	19.0 ± .476 (20)		19.5 ± .515 (20)		20.6 ± .504 (20)		19.6 ± .587 (20)	
WEEK 1	*	20.5 ± .806 (20)	19.8 ± .605 (20)		18.3 ± .508 (20)	*	17.3 ± .620 (20)	*	15.2 ± .384 (18)	+ A
WEEK 2	+	22.2 ± .919 (20)	21.3 ± .719 (20)		19.1 ± .655 (19)	*	18.2 ± .714 (20)	*	14.5 ± .291 (15)	+ B
WEEK 3	*	20.3 ± .883 (20)	22.0 ± .884 (20)		20.6 ± .663 (19)		19.6 ± .903 (19)		15.4 ± .359 (14)	+ A
WEEK 4	*	23.0 ± .875 (19)	23.5 ± .950 (19)		22.2 ± .660 (19)		20.1 ± .961 (19)	*	17.2 ± .423 (12)	+ A
WEEK 5		24.3 ± .942 (19)	24.3 ± .968 (19)		22.7 ± .750 (19)		21.7 ± .983 (18)		16.8 ± .629 (10)	+ A
WEEK 6	*	25.0 ± .940 (19)	25.6 ± .918 (19)		21.5 ± .723 (19)	*	22.6 ± 1.11 (18)		17.7 ± .473 (10)	+ B
WEEK 7	*	27.4 ± .931 (19)	26.5 ± .899 (19)		24.6 ± .672 (19)	*	25.2 ± 1.17 (18)		21.7 ± .616 (10)	+ A
WEEK 8		27.5 ± .853 (19)	26.4 ± .773 (19)		25.3 ± .730 (19)		23.7 ± .966 (18)	*	21.5 ± .719 (10)	+ A
WEEK 9	*	29.2 ± .886 (19)	29.3 ± .809 (19)		26.9 ± .723 (19)		25.7 ± 1.26 (18)	*	23.1 ± .657 (10)	+ A
WEEK 10	*	29.2 ± .819 (19)	29.4 ± .710 (19)		27.6 ± .742 (19)		26.9 ± 1.32 (18)		24.0 ± .699 (10)	+ A
WEEK 11	*	29.9 ± .878 (19)	28.9 ± .731 (19)		27.6 ± .807 (19)		26.7 ± 1.34 (18)		22.7 ± .578 (10)	+ A
WEEK 12	*	29.4 ± 1.30 (19)	31.5 ± .739 (19)		29.2 ± .867 (19)		29.2 ± 1.36 (18)		24.8 ± .742 (10)	*
WEEK 13	*	31.4 ± .896 (19)	30.9 ± .729 (19)		29.6 ± .889 (19)		29.2 ± 1.36 (18)		26.4 ± .618 (10)	+

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
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20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 229

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHTS (G)
OF MALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R	.50 % IN DIET	T R
WEEK 1		.4 ± .686 (20)	2.8 ± .557 (20)	•	-.4 ± .600 (20)	•	-3.2 ± .650 (20)	+ •	-3.3 ± .405 (20)	+ •
WEEK 2	*	1.3 ± .583 (19)	2.0 ± .394 (20)		2.0 ± .805 (20)		.3 ± .636 (20)		-.1 ± .467 (14)	B
WEEK 3	+	-1.6 ± .871 (18)	1.2 ± .551 (20)	* •	1.5 ± .626 (20)	* •	1.6 ± .499 (20)	* •	1.9 ± .211 (13)	+ •
WEEK 4	+	5.6 ± .977 (17)	1.8 ± .533 (19)	* C	1.5 ± .303 (20)	+ D	.4 ± .406 (20)	+ D	2.4 ± .358 (12)	* C
WEEK 5		1.5 ± .322 (17)	1.5 ± .435 (19)		1.3 ± .398 (20)		1.5 ± .336 (20)		.8 ± .386 (12)	
WEEK 6	*	.9 ± .363 (17)	.8 ± .210 (19)		.6 ± .232 (20)		.2 ± .277 (20)		1.1 ± .557 (12)	
WEEK 7	*	.9 ± .348 (17)	2.9 ± .259 (19)	+	2.5 ± .246 (20)	+	2.6 ± .275 (20)	+	3.4 ± .773 (12)	*
WEEK 8	+	1.8 ± .291 (17)	-1.3 ± .297 (19)	+ D	-.3 ± .239 (20)	+ D	-.3 ± .302 (20)	+ D	.1 ± .839 (12)	
WEEK 9	+	.5 ± .259 (17)	2.7 ± .274 (19)	+ •	2.0 ± .492 (20)	* •	1.7 ± .252 (20)	* •	1.2 ± .661 (12)	•
WEEK 10		.5 ± .244 (17)	.3 ± .367 (19)	•	.4 ± .351 (20)	•	1.5 ± .380 (20)	•	.8 ± .641 (12)	•
WEEK 11		.9 ± .469 (17)	-.7 ± .606 (19)	•	-.6 ± .493 (20)	•	-.3 ± .398 (20)	•	-.3 ± .450 (12)	•
WEEK 12	+	.4 ± .636 (17)	1.7 ± .500 (19)	•	1.1 ± .575 (20)	•	2.4 ± .275 (20)	* •	1.7 ± .256 (12)	•
WEEK 13	+	.8 ± .338 (17)	-.2 ± .414 (19)		2.0 ± .692 (20)		.3 ± .219 (20)		1.4 ± .288 (12)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
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R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 230

EFFECTS OF LAP ON DIFFERENCES IN BODY WEIGHTS (G)
OF FEMALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R	.50 % IN DIET	T R
WEEK 1		.9 ± .324 (20)	.8 ± .401 (20)	•	-1.3 ± .527 (20)	* •	-3.3 ± .509 (20)	+ •	-4.5 ± .567 (18)	+ •
WEEK 2		1.6 ± .493 (20)	1.5 ± .295 (20)		.7 ± .433 (19)		.9 ± .294 (20)		-1.1 ± .412 (15)	+ D
WEEK 3		-1.9 ± .458 (20)	.8 ± .307 (20)	+ •	1.6 ± .353 (19)	+ •	1.3 ± .284 (19)	+ •	.8 ± .447 (14)	+ •
WEEK 4	+	2.3 ± .834 (19)	1.1 ± .223 (19)	A	1.6 ± .139 (19)		.5 ± .193 (19)	* D	1.4 ± .398 (12)	
WEEK 5	+	1.3 ± .577 (19)	.8 ± .233 (19)		.5 ± .328 (19)		1.2 ± .146 (18)		-.7 ± .307 (10)	* D
WEEK 6		.7 ± .323 (19)	1.3 ± .217 (19)		-1.2 ± .344 (19)	+ D	.9 ± .241 (18)		.9 ± .233 (10)	
WEEK 7		2.4 ± .279 (19)	.9 ± .285 (19)	* C	3.1 ± .370 (19)		2.6 ± .315 (18)		4.0 ± .494 (10)	
WEEK 8		.1 ± .291 (19)	-.2 ± .299 (19)	•	.7 ± .323 (19)	•	-1.4 ± .437 (18)	•	-.2 ± .573 (10)	•
WEEK 9	*	1.7 ± .297 (19)	2.9 ± .247 (19)	*	1.6 ± .191 (19)		1.9 ± .357 (18)		1.6 ± .163 (10)	
WEEK 10	*	.1 ± .366 (19)	.1 ± .252 (19)	•	.7 ± .203 (19)	•	1.2 ± .207 (18)	* •	.9 ± .407 (10)	•
WEEK 11		.7 ± .267 (19)	-.5 ± .354 (19)	•	-.1 ± .527 (19)	•	-.2 ± .459 (18)	•	-1.3 ± .423 (10)	•
WEEK 12	+	-.5 ± .965 (19)	2.6 ± .414 (19)	*	1.6 ± .406 (19)		2.4 ± .697 (18)	*	2.1 ± .458 (10)	*
WEEK 13	+	1.9 ± .987 (19)	-.6 ± .244 (19)	* •	.4 ± .176 (19)	•	0.0 ± .616 (18)	•	1.6 ± .340 (10)	•

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - • .

TABLE 231

EFFECTS OF LAP ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .005 %	0.05 %	0.25 %	0.5 %
WEEK 1	3.06	3.95	3.24	2.67	2.09
WEEK 2	4.42	4.77	4.01	3.35	2.73
WEEK 3	3.11	4.86	4.08	3.46	3.84
WEEK 4	4.87	5.14	4.11	3.39	4.65
WEEK 5	4.88	5.85	4.66	4.15	4.62
WEEK 6	4.86	5.53	4.89	4.31	6.63
WEEK 7	4.56	5.71	4.96	4.99	6.24
WEEK 8	4.84	5.18	4.51	4.72	6.10
WEEK 9	5.45	5.86	5.01	5.99	6.24
WEEK 10	5.13	5.78	4.87	5.27	5.71
WEEK 11	5.08	5.26	4.57	3.95	5.38
WEEK 12	5.31	5.82	4.79	4.74	5.44
WEEK 13	5.36	5.62	5.26	4.70	5.65

ENTRIES ARE MEANS. GROUP N SAME AS IN BODY WEIGHT TABLES.

TABLE 232

EFFECTS OF LAP ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .005 %	0.05 %	0.25 %	0.5 %
WEEK 1	3.37	3.14	3.28	2.78	1.97
WEEK 2	3.70	3.86	3.12	3.43	2.25
WEEK 3	3.25	3.71	3.75	3.58	2.81
WEEK 4	4.21	3.93	3.74	4.16	3.83
WEEK 5	4.33	4.72	4.26	4.20	2.92
WEEK 6	4.27	4.53	4.50	4.40	5.57
WEEK 7	4.15	5.11	4.72	5.04	8.07
WEEK 8	4.20	4.10	4.39	4.70	6.46
WEEK 9	4.61	4.80	4.62	5.60	7.31
WEEK 10	4.47	4.71	4.56	5.10	7.11
WEEK 11	4.08	4.01	4.00	4.42	5.31
WEEK 12	4.22	4.82	4.38	4.72	6.39
WEEK 13	4.68	4.73	4.28	4.65	6.72

ENTRIES ARE MEANS. GROUP N SAME AS IN BODY WEIGHT TABLES.

TABLE 233

EFFECTS OF LAP ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF MALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	W	.05 % IN DIET	W	.25 % IN DIET	W	.5 % IN DIET	W
WEEK 1	136.0 ± 5.78 (4)	156.6 ± 8.38 (4)		154.1 ± 6.46 (4)		148.1 ± 8.79 (4)		129.5 ± 17.6 (4)	
WEEK 2	180.0 ± 19.7 (4)	175.1 ± 6.01 (4)		173.4 ± 9.98 (4)		184.4 ± 8.85 (4)		171.1 ± 19.0 (4)	
WEEK 3	135.3 ± 5.26 (4)	170.4 ± 6.86 (4)		138.6 ± 34.9 (4)		174.5 ± 7.97 (4)		207.9 ± 31.1 (4)	
WEEK 4	168.1 ± 8.56 (4)	168.0 ± 13.4 (4)		157.0 ± 10.4 (4)		192.9 ± 5.91 (4)		222.9 ± 38.4 (4)	
WEEK 5	161.3 ± 8.73 (4)	181.9 ± 7.70 (4)		170.2 ± 8.89 (4)		191.4 ± 5.59 (4)		212.0 ± 19.7 (4)	
WEEK 6	155.7 ± 8.62 (4)	167.9 ± 4.78 (4)		174.6 ± 8.95 (4)		198.2 ± 9.57 (4)		245.2 ± 81.9 (4)	
WEEK 7	139.9 ± 16.1 (4)	158.7 ± 7.37 (4)		163.0 ± 9.66 (4)		203.9 ± 5.50 (4)		237.3 ± 41.0 (4)	
WEEK 8	143.0 ± 7.74 (4)	150.0 ± 5.21 (4)		149.1 ± 8.69 (4)		196.9 ± 14.3 (4)		229.8 ± 42.8 (4)	
WEEK 9	157.9 ± 10.8 (4)	156.9 ± 5.39 (4)		155.6 ± 12.6 (4)		232.2 ± 8.97 (4)		225.6 ± 45.4 (4)	
WEEK 10	146.1 ± 9.83 (4)	153.8 ± 3.59 (4)		148.7 ± 11.3 (4)		192.9 ± 7.06 (4)		201.2 ± 22.4 (4)	
WEEK 11	141.5 ± 9.39 (4)	142.7 ± 5.39 (4)		143.4 ± 8.02 (4)		146.0 ± 6.85 (4)		191.4 ± 19.8 (4)	
WEEK 12	145.3 + 5.01 (3)	150.7 ± 3.54 (4)		144.9 ± 4.31 (4)		161.1 ± 4.69 (4)		182.5 ± 23.3 (4)	
WEEK 13	165.5 ± 6.11 (4)	168.8 ± 3.74 (4)		169.9 ± 10.8 (4)		180.3 ± 13.5 (4)		207.2 ± 22.2 (4)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 234

EFFECTS OF LAP ON FOOD CONSUMPTION (G/KG (BODY WT)/DAY)
OF FEMALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP		TREATMENT GROUPS: .005 % IN DIET		W	.05 % IN DIET		W	.25 % IN DIET		W	.5 % IN DIET		W
WEEK 1	164.1 ± 4.71	(4)	157.1 ± 9.50	(4)		178.5 ± 10.2	(4)		158.9 ± 10.5	(4)		129.8 ± 15.4	(4)	
WEEK 2	167.1 ± 3.83	(4)	180.1 ± 9.53	(4)		164.4 ± 7.40	(4)		186.2 ± 7.42	(4)		155.0 ± 11.0	(4)	
WEEK 3	159.3 ± 9.60	(4)	166.4 ± 11.5	(4)		182.0 ± 6.95	(4)		181.8 ± 7.29	(4)		183.5 ± 15.1	(4)	
WEEK 4	183.3 ± 6.57	(4)	166.4 ± 13.2	(4)		167.7 ± 6.21	(4)		206.9 ± 5.92	(4)		221.7 ± 22.5	(4)	
WEEK 5	178.4 ± 3.04	(4)	194.3 ± .646	(4)		186.1 ± 5.17	(3)		195.4 ± 3.43	(4)		171.3 ± 34.0	(4)	
WEEK 6	170.9 ± 1.37	(4)	176.4 ± 7.83	(4)		208.9 ± 9.21	(4)		197.8 ± 13.5	(4)		311.9 ± 61.9	(4)	*
WEEK 7	151.5 ± 6.91	(4)	192.9 ± 5.55	(4)		192.1 ± 8.07	(4)		201.2 ± 8.59	(4)		371.0 ± 82.4	(4)	*
WEEK 8	153.2 ± 5.97	(4)	155.0 ± 5.53	(4)		173.0 ± 4.83	(4)		198.9 ± 16.5	(4)		298.3 ± 54.4	(4)	*
WEEK 9	157.8 ± 3.19	(4)	163.6 ± 1.82	(4)		171.0 ± 5.64	(4)		220.3 ± 12.9	(4)		315.9 ± 62.2	(4)	*
WEEK 10	152.8 ± 6.25	(4)	160.3 ± 5.78	(4)		164.8 ± 7.47	(4)		192.5 ± 14.3	(4)		292.2 ± 67.9	(4)	*
WEEK 11	136.2 ± 1.72	(4)	138.2 ± 2.48	(4)		144.9 ± 1.80	(4)		167.9 ± 13.0	(4)		230.7 ± 48.3	(4)	
WEEK 12	143.2 ± 1.77	(4)	152.7 ± 3.72	(4)		150.0 ± 4.67	(4)		163.3 ± 7.63	(4)		253.4 ± 49.3	(4)	*
WEEK 13	161.4 ± 10.3	(4)	200.7 ± 35.1	(4)		158.3 ± 6.38	(4)		184.9 ± 23.8	(4)		269.5 ± 60.8	(4)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

TABLE 235

DOSES OF LAP (MG/KG (BODY WT)/DAY) IN DIETS CONSUMED BY MALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS .005 % IN DIET	.05 % IN DIET	.25 % IN DIET	.50 % IN DIET
WEEK 1	7.83	77.06	370.2	647.3
WEEK 2	8.76	86.68	460.9	855.3
WEEK 3	8.52	69.28	436.2	1039.6
WEEK 4	8.40	78.49	482.2	1114.7
WEEK 5	9.10	85.10	478.4	1060.1
WEEK 6	8.39	87.28	495.5	1226.0
WEEK 7	7.94	81.48	509.7	1186.6
WEEK 8	7.50	74.56	492.4	1149.0
WEEK 9	7.84	77.82	580.4	1128.0
WEEK 10	7.69	74.36	482.3	1006.1
WEEK 11	7.14	71.70	365.1	956.9
WEEK 12	7.54	72.45	402.8	912.5
WEEK 13	8.44	84.96	450.7	1036.2

TABLE 236

DOSES OF LAP (MG/KG (BODY WT)/DAY) IN DIETS CONSUMED BY FEMALE MICE DURING 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS .005 % IN DIET	.05 % IN DIET	.25 % IN DIET	.50 % IN DIET
WEEK 1	7.86	89.23	397.2	649.0
WEEK 2	9.01	82.22	465.5	77[illegible].0
WEEK 3	8.32	91.02	454.4	917.3
WEEK 4	8.32	83.85	517.3	1108.3
WEEK 5	9.71	93.04	488.6	856.6
WEEK 6	8.82	104.46	494.6	1559.3
WEEK 7	9.64	96.07	502.9	1854.8
WEEK 8	7.75	86.50	497.2	1491.4
WEEK 9	8.18	85.50	550.7	1579.4
WEEK 10	8.02	82.39	481.3	1461.[illegible]
WEEK 11	6.91	72.44	419.8	1153.4
WEEK 12	7.64	75.00	408.3	1267.2
WEEK 13	10.03	79.17	462.3	1347.3

TABLE 237

EFFECTS OF LAF ON ORGAN WEIGHTS (G)
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE MICE AFTER 13 WEEKS OF TREATMENT

			TREATMENT GROUPS							
DEPENDENT VARIABLE	B C	CONTROL GROUP	.005 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R	.50 % IN DIET	T R
FINAL WT (G)		37.44 ± 1.14 (16)	38.42 ± .589 (19)		35.10 ± .900 (20)		29.75 ± 1.10 (20)	+ A	30.57 ± .894 (14)	+ A
BRAIN		.55 ± .009 (17)	.55 ± .015 (19)		.51 ± .009 (20)		.48 ± .012 (20)	+ A	.49 ± .012 (12)	
HEART		.22 ± .011 (17)	.25 ± .011 (19)	A	.22 ± .011 (20)		.18 ± .009 (20)	A	.19 ± .010 (12)	A
KIDNEYS		.63 ± .029 (17)	.67 ± .028 (19)		.61 ± .025 (20)		.52 ± .022 (20)		.54 ± .017 (12)	
LIVER		2.24 ± .103 (17)	2.26 ± .060 (19)		2.12 ± .091 (20)		1.89 ± .083 (20)		2.32 ± .098 (12)	
SPLEEN	*	.15 ± .009 (17)	.17 ± .020 (19)		.15 ± .012 (20)		.18 ± .015 (20)	*	.21 ± .024 (12)	*
TESTES		.25 ± .011 (17)	.24 ± .010 (19)		.25 ± .009 (20)		.23 ± .008 (20)		.24 ± .008 (12)	
BRAIN/BODY		14.88 ± .386 (16)	14.22 ± .334 (19)		14.68 ± .336 (20)		16.52 ± .554 (20)		16.10 ± .547 (12)	
HEART/BODY		5.92 ± .281 (16)	6.54 ± .292 (19)		6.26 ± .258 (20)		6.17 ± .208 (20)		6.10 ± .279 (12)	
KIDNEY/BODY		17.05 ± .535 (16)	17.53 ± .661 (19)		17.24 ± .500 (20)		17.65 ± .345 (20)		17.50 ± .464 (12)	
LIVER/BODY		60.21 ± 1.53 (16)	58.93 ± 1.59 (19)		60.21 ± 1.63 (20)		63.61 ± 1.70 (20)		75.17 ± 3.09 (12)	+ A
SPLEEN/BODY	+	3.79 ± .226 (16)	4.63 ± .632 (19)		4.28 ± .305 (20)		6.24 ± .566 (20)	+ B	6.84 ± .720 (12)	+ B
TESTES/BODY		6.60 ± .210 (16)	6.25 ± .242 (19)		7.10 ± .177 (20)		7.98 ± .276 (20)	+	7.90 ± .335 (12)	*
HEART/BRAIN		.40 ± .019 (17)	.46 ± .019 (19)	A	.43 ± .019 (20)		.38 ± .016 (20)		.38 ± .016 (12)	
KIDNEY/BRAIN		1.15 ± .046 (17)	1.23 ± .042 (19)		1.18 ± .034 (20)		1.08 ± .031 (20)		1.10 ± .038 (12)	
LIVER/BRAIN		4.07 ± .157 (17)	4.16 ± .101 (19)		4.14 ± .147 (20)		3.90 ± .115 (20)		4.70 ± .193 (12)	
SPLEEN/BRAIN	+	.27 ± .017 (17)	.33 ± .048 (19)		.29 ± .021 (20)		.38 ± .029 (20)	* A	.43 ± .044 (12)	* A
TESTES/BRAIN		.46 ± .018 (17)	.44 ± .016 (19)		.49 ± .016 (20)		.49 ± .012 (20)		.49 ± .019 (12)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - [illegible] .

TABLE 238

EFFECTS OF LAP ON ORGAN WEIGHTS (G)
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE MICE AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	.005 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R	.50 % IN DIET	T R
			TREATMENT GROUPS							
FINAL WT (G)	*	31.37 ± .896 (19)	30.89 ± .729 (19)		29.63 ± .889 (19)		29.17 ± 1.36 (18)		26.40 ± .618 (10)	+
BRAIN		.54 ± .013 (19)	.54 ± .013 (19)		.51 ± .012 (19)		.50 ± .016 (18)		.46 ± .011 (10)	* A
HEART		.17 ± .008 (19)	.18 ± .007 (19)		.16 ± .007 (19)		.17 ± .011 (18)		.15 ± .010 (10)	A
KIDNEYS	*	.45 ± .017 (19)	.45 ± .014 (19)		.40 ± .016 (19)	*	.39 ± .024 (18)		.34 ± .012 (10)	+ A
LIVER	+	1.88 ± .068 (19)	1.89 ± .064 (19)		1.73 ± .072 (19)		2.05 ± .141 (18)		1.92 ± .075 (10)	
SPLEEN	+	.14 ± .008 (19)	.13 ± .010 (19)		.13 ± .006 (19)		.22 ± .028 (18)	* A	.19 ± .015 (10)	*
BRAIN/BODY		17.36 ± .529 (19)	17.48 ± .445 (19)		17.32 ± .483 (19)		17.56 ± .555 (18)		17.70 ± .602 (10)	
HEART/BODY		5.47 ± .177 (19)	5.75 ± .207 (19)		5.38 ± .169 (19)		5.72 ± .202 (18)		5.69 ± .360 (10)	
KIDNEY/BODY		14.29 ± .467 (19)	14.71 ± .401 (19)		13.40 ± .349 (19)		13.35 ± .371 (18)		13.07 ± .576 (10)	
LIVER/BODY		59.78 ± 1.17 (19)	61.09 ± 1.38 (19)		58.03 ± 1.36 (19)		69.22 ± 1.92 (18)	+	73.04 ± 2.95 (10)	+ A
SPLEEN/BODY	+	4.39 ± .202 (19)	4.27 ± .296 (19)		4.43 ± .186 (19)		7.15 ± .628 (18)	+ B	7.16 ± .524 (10)	+ B
HEART/BRAIN		.32 ± .013 (19)	.33 ± .014 (19)		.31 ± .013 (19)		.33 ± .015 (18)		.33 ± .023 (10)	
KIDNEY/BRAIN		.83 ± .022 (19)	.84 ± .016 (19)		.78 ± .025 (19)		.77 ± .030 (18)		.74 ± .027 (10)	
LIVER/BRAIN		3.49 ± .119 (19)	3.52 ± .101 (19)		3.40 ± .127 (19)		4.03 ± .191 (18)		4.17 ± .246 (10)	
SPLEEN/BRAIN	+	.26 ± .014 (19)	.24 ± .016 (19)		.26 ± .011 (19)		.42 ± .044 (18)	* B	.41 ± .039 (10)	* B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 239

EFFECTS OF LAP ON HEMATOLOGY
OF MALE MICE AFTER 13 WEEKS OF TREATMENT

			TREATMENT GROUPS							
DEPENDENT VARIABLE	B C	CONTROL GROUP	.005 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R	.50 % IN DIET	T R
RBC (X 10^6)	*	6.98 ± .273 (13)	7.25 ± .367 (15)		6.95 ± .146 (16)		6.33 ± .140 (16)	*	6.05 ± .297 (9)	*
HGB (G %)	+	14.03 ± .367 (13)	13.97 ± .615 (15)		14.01 ± .167 (16)		13.23 ± .228 (16)		12.34 ± .405 (9)	*
HCT (%)	+	34.82 ± 1.38 (13)	35.82 ± 2.00 (15)		33.76 ± .868 (16)		31.64 ± .546 (16)	*	30.62 ± 1.30 (9)	*
MCV $(U)^3$		52.31 ± .570 (13)	52.07 ± .605 (15)		51.81 ± .449 (16)		53.50 ± .474 (16)		53.44 ± 1.02 (9)	
MCH (UUG)	+	20.55 ± .558 (13)	18.08 ± 1.21 (15)		20.51 ± .383 (16)		21.05 ± .333 (16)		20.93 ± .537 (9)	
MCHC (%)		41.18 ± 1.25 (13)	39.21 ± 1.25 (15)		41.97 ± .855 (16)		42.31 ± 1.05 (16)		41.28 ± 1.33 (9)	
WBC (X 10^3)		10.15 ± .916 (13)	8.73 ± .813 (15)		11.82 ± .716 (16)		10.23 ± .785 (16)		13.91 ± 1.48 (9)	
PMN (%)	*	26.33 ± 3.87 (12)	35.33 ± 3.20 (15)		28.50 ± 1.85 (16)		21.00 ± 1.42 (16)		23.00 ± 2.13 (9)	
BANDS (%)		.33 ± .188 (12)	1.47 ± .192 (15)	+ *	.81 ± .188 (16)	*	.53 ± .165 (15)	*	1.00 ± .167 (9)	*
LYMPH (%)	*	66.67 ± 4.29 (12)	56.53 ± 3.12 (15)		61.94 ± 1.97 (16)		70.81 ± 1.53 (16)		69.22 ± 2.56 (9)	
MONO (%)	*	3.08 ± .621 (12)	4.73 ± .483 (15)	*	3.19 ± .277 (16)		3.00 ± .376 (16)		4.44 ± .242 (9)	
EOSIN (%)		2.92 ± .557 (12)	1.13 ± .306 (15)	B	4.50 ± .563 (16)		3.44 ± .456 (16)		1.56 ± .412 (9)	
BASO (%)		0.00 ± 0.00 (12)	0.00 ± 0.00 (15)		0.00 ± 0.00 (12)		0.00 ± 0.00 (12)		0.00 ± 0.00 (9)	
ATYP LYMPH(%)		.92 ± .269 (12)	.80 ± .312 (15)		1.13 ± .202 (16)		1.27 ± .248 (15)		.67 ± .289 (9)	
RETICS (%)	+	.96 ± .117 (13)	1.67 ± .599 (15)		1.09 ± .116 (15)		5.61 ± .711 (14)	+ D	12.44 ± 1.69 (9)	+ D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

TABLE 240

EFFECTS OF LAP ON HEMATOLOGY
OF FEMALE MICE AFTER 13 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	TREATMENT GROUPS .005 % IN DIET	T R	.05 % IN DIET	T R	.25 % IN DIET	T R	.50 % IN DIET	T R
RBC (X 10^6)	+	7.43 ± .348 (14)	7.61 ± .134 (16)		7.16 ± .183 (16)		6.66 ± .125 (16)		6.49 ± .178 (9)	*
HGB (G %)		14.62 ± .324 (14)	14.79 ± .203 (16)		14.27 ± .193 (16)		14.04 ± .193 (16)		13.87 ± .437 (9)	
HCT (%)	*	37.29 ± 1.99 (14)	38.13 ± 1.00 (16)		35.02 ± 1.14 (16)		33.44 ± .877 (16)		32.62 ± 1.16 (9)	
MCV (U)3		51.00 ± .469 (14)	51.44 ± .456 (16)		51.37 ± .427 (16)		52.31 ± .395 (16)		51.89 ± .588 (9)	
MCH (UUG)		20.02 ± .541 (14)	19.67 ± .355 (16)		20.19 ± .454 (16)		21.24 ± .459 (16)		21.44 ± .383 (9)	
MCHC (%)		39.96 ± 1.38 (14)	39.64 ± .971 (16)		41.49 ± 1.16 (16)		42.45 ± 1.35 (16)		42.91 ± 1.43 (9)	
WBC (X 10^3)		8.12 ± .925 (14)	9.93 ± .774 (16)		9.13 ± .972 (16)		11.73 ± .806 (16)		14.11 ± 1.67 (9)	+ B
PMN (%)		17.93 ± 1.89 (14)	20.93 ± 1.76 (15)		15.[illegible]5 ± 1.20 (16)		17.19 ± 1.54 (16)		18.25 ± 1.73 (8)	
BANDS (%)		.23 ± .122 (13)	.73 ± .153 (15)	*	.07 ± .071 (14)	*	.23 ± .166 (13)	*	.25 ± .164 (8)	*
LYMPH (%)		74.86 ± 2.57 (14)	70.73 ± 2.00 (15)		75.50 ± 1.55 (16)		75.50 ± 1.56 (16)		73.25 ± 2.39 (8)	
MONO (%)		2.64 ± .476 (14)	4.87 ± .376 (15)	+ B	3.31 ± .254 (16)		3.00 ± .258 (16)		4.63 ± .420 (8)	* A
EOSIN (%)	*	3.43 ± .823 (14)	1.67 ± .454 (15)	A	5.00 ± .707 (16)		3.13 ± .328 (16)		2.50 ± .567 (8)	
BASO (%)		0.00 ± 0.00 (14)	0.00 ± 0.00 (15)		0.00 ± 0.00 (4)		0.00 ± 0.00 (10)		0.00 ± 0.00 (8)	
ATYP LYMPH(%)		1.00 ± .182 (14)	1.07 ± .300 (15)		1.00 ± .224 (16)		1.14 ± .206 (14)		1.13 ± .479 (8)	
RETICS (%)	+	.84 ± .063 (14)	1.21 ± .107 (15)	*	1.22 ± .099 (16)	* A	4.07 ± .445 (15)	+ D	9.46 ± 2.35 (8)	* D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
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R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A
20 % - B, 33 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - * .

Table 241

MICROSCOPIC LESIONS IN MALE MICE AFTER 13 WEEKS OF LAP TREATMENT

Organ/Lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.25	0.50
	Group Designation				
	B0	B1	B2	B3	B4 *
	Animal Number				
Adrenals					
Congestion - inner cortex				363	
Fibrosis - midcortex	302,320				
Colon					
Parasitism - nematode	302			362,363,364	384,385,391
				366,367,368	392,398
				369,373,375	
				376,377,380	
Eye					
Atrophy (absence of rods and cones)	315			362	
Ileum					
Parasitism				378	390,400
Parasitism	317			363,365,367	
				369,370,375	
Kidney					
Lymphocytes - interstitial	310,315			375	
Lymphocytes - paravascular	302,303,305			363,368,369	
	309,310,311			372,374,375	
	313,315,319			380	
	320				
Liver					
Lymphocytes - parenchymal				364,371,372	
				374,375,377	
				378,379	
Lymphocytes - WBC parenchymal, parenchymal				376	
Lung					
Alveolar collapse, alveolar dilation	312				
Alveolar histiocytosis	319				

* Nos. 390 and 395 died during week 2; No. 396 died during week 4.

Table 241 (Continued)

Organ/Lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.25	0.50
	Group Designation				
	B0	B1	B2	B3	B4
	Animal Number				
Alveolar tumor				307	
Congestion	305,306,310			370,378,379	
	311				
Respiratory disease - chronic	302,303,305			361,363,365	382,383,385
	308,309,310			366,367,369	387,390,392
				372,373,380	395,396
Alveolar collapse, alveolar dilation,					
ectasia (dilated), bronchosis	317				
Alveolar collapse, alveolar dilation,					
hemorrhage					399
Alveolar histiocytosis, respiratory					
disease - chronic	301				
Respiratory disease - chronic, congestion	313,315			374	
Respiratory disease - chronic, acute					
inflammation				368,370,371	
Respiratory disease - chronic, chronic					
inflammation					384
Respiratory disease - chronic, phages,					
lymphocytes - parenchymal - pigmented				362	
Respiratory disease - chronic,					
pneumonia broncho				377	391,395
Pneumonia, broncho					400
Pneumonia, broncho, respiratory disease -					
chronic, congestion, edema					398
Lymph nodes					
Hyperplasia - R.E. cells				361	
Granuloma, hemorrhage (old)				363	

Table 241 (Concluded)

Organ/Lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.25	0.50
	Group Designation				
	B0	B1	B2	B3	B4
	Animal Number				
Salivary gland					
Lymphocytes - paravascular				368,374	387,398,395
Skin					
Acanthiosis	316				
Inflammation - subacute (dermis)	310				
Inflammation - subacute (muscle underlying skin)				371	
Inflammation - chronic (muscle underlying skin), Inflammation - subacute (dermis)	309				
Spleen					
Pigmentation (hemosiderosis)	311,320	323,325	342,343,344 347,349,354 355,356,357 358,359,360	362,363,364 365,366,367 368,369,370 371,372,373 374,375,376 377,378,379 380	382,383,384 385,387,390 391,392,393 395,398,399 400
Thymus					
Hemorrhage	312				
Trachea					
Pus in trachea				377	

MICROSCOPIC LESIONS IN FEMALE MICE AFTER 13 WEEKS OF LAP TREATMENT

Organ/lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.25	0.50
	Group Designation				
	B0	B1	B2	B3	B4
	Animal Number				
Adrenals					
Congestion - inner cortex	408,410,417			478,479	490
Fibrosis - midcortex	405			476	
Hyperplasia - outer cortex	414				
Congestion - inner cortex and fibrosis, midcortex	416				
Colon					
Parasitism - nematode	405,410			461,469,474	
	414,415			476	
Eye					
Atrophy (Absence of rods and cones)	417				
Heart					
Lymphocytes - interstitial				466	
Calcification, slight focal					499
Ileum					
Parasitism				461,472,475	482,496,497
				477	
Parasitism - nematode	403				
Kidney					
Lymphocytes - paravascular	401,402,405			461,462,463	496,499
	406,407,408			466	
	409,411,412				
	414,416,421				
Liver					
Lymphocytes - parenchymal	403,406,408			463,468,469	484,490
	410,414			471,476,474	
				480	

Table 242 (continued)

Organ/Lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.25	0.50
	Group Designation				
	B0	B1	B2	B3	B4
	Animal Number				
Liver (continued)					
Lymphocytes - WBC paravascular, paravascular	405				
Lymphocytes - parenchymal and necrosis					482
Lung					
Alveolar collapse					482
Alveolar collapse and alveolar dilation	417				
Congestion	403,404			478	
Hemorrhage				479	
Lymphocytes - interstitial - WBC stromal				477	
Pneumonia, broncho					484,488
Respiratory disease - chronic	409			461,462,468 474	496,499
Alveolar collapse, alveolar dilation, lymphocytes - interstitial - pneumonitis					490
Hemorrhage, lymphocytes - interstitial - pneumonitis					494
Alveolar collapse, alveolar dilation, respiratory disease - chronic	405,410			472,475	433
Respiratory disease - chronic, congestion	406,408			476	
Respiratory disease - chronic, hemorrhage				480	
Respiratory disease - chronic, acute inflammation				464,471	
Respiratory disease - chronic, pneumonia, broncho					498
Alveolar collapse, alveolar dilation, ectasia (dilation) bronchioles respiratory disease - chronic	421				

Organ/Lesion	Dose Level (% in Feed)				
	0	0.005	0.05	0.025	0.50
	Group Designation				
	B0	B1	B2	B3	B4
	Animal Number				
Lymph nodes					
Granuloma	413				483,494,499
Hyperplasia - R.E. cells	410			466,469	
Granuloma, hemorrhage (old)					497
Salivary gland					
Lymphocytes - paravascular	404,406,415			469,471,474	499
	416,417				
Skin					
Inflammation - chronic	414				
Spleen					
Pigmentation (hemosiderosis)	401,403,404	422,426,427	442,443,445	461,462,463	483,484
	406,407,408	428,431,433	447,448,449	464,466,467	490,494,496
	409,410	435,439	450,451,452	468,469,470	497,498,499
			453,454,455	472,476,477	
			457,458,460	478,480	
Trachea					
Pus in trachea					484
Uterus					
Chronic inflammation of mucosa	406				
Hyperplasia of mucosa in 1 horn					490
Hyperplasia of mucosa in both horns					494
Vagina					
Acute inflammation of mucosa	417			463,464,479	482,498
				480	

PART 4 - SUBACUTE ORAL TOXICITY STUDIES ON LAP(I) (PHASE II)

INTRODUCTION

This section describes the results of a 28-day subacute oral toxicity study of LAP(I) in rats. The study was conducted (1) to define the toxicological response of these animals to repeated doses of the irradiated mixture and (2) to compare its potency with that of the unirradiated mixture from which it was prepared.

PROCEDURES

A total of 104 Sprague-Dawley rats (approximately 6 to 7 weeks old, equal number of each sex) were received from Simonsen Laboratories and divided into five groups as follows. To assign animals to groups, all the rats of each sex were weighed and placed in cages by weight, each cage covering a range of 5 g in body weight. After all the rats were distributed in this way, the number in each weight range was counted and redistributed among the dose level groups, starting with the lowest weights first and working upward to the highest, in such a way as to yield approximately equal mean body weights for each group. The animals were marked, reweighed, and placed in their new cages (three followed by two to a cage) for the experiment. Each experimental group consisted of 10 males and 10 females; the extras were discarded.

The treatment and dose levels for the groups were as follows:

- LAP(I) at 0.003, 0.03, and 0.3% by weight in the diet;
- LAP at 0.3% by weight in the diet, serving as a reference and positive control;
- Negative control group, fed the same rodent chow untreated.

A diet containing 0.3% LAP(I) in the feed was prepared by mixing 34.5 g of the irradiated mixture with 11,465.5 g of the powdered chow* in a large rotary mixer for 15 minutes. A portion of this diet was

* Powdered Purina Rodent Laboratory Chow 5001.

further diluted with the chow to form the 0.03% LAP(I) diet in the mixer. The procedure was repeated, using a portion of the 0.03% LAP(I) diet to form the low dose. The LAP diet was prepared as described in Part 3 Procedures. All treated diets were made up fresh biweekly and stored in tightly capped polyethylene containers in a dark refrigerator until use. The diets were given to the rats in covered hanging feeders within their cages. Food additions or changes were made weekly. Water was available <u>ad libitum</u>.

Animal identification procedures, the quarantine period, animal housing, test methods (body weight, food consumption, organ weights, hematology, blood chemistry, and histopathology) were as described in Part 2 Procedures, except that the blood chemistry determinations were made at SRI by the methods described in Appendix A.

The rats were deprived of food for at least 16 hours prior to sacrifice. Immediately before sacrifice, each rat was injected i.p. with $\geq$ 0.5 ml of Pentothal (sodium thiopental). After anesthetization, approximately 8 cc of blood was withdrawn by cardiac puncture directly into a 10-cc syringe and transferred in two portions into a 2-ml Vacutainer with EDTA additive for hematological analysis (CBC, including reticulocytes, hemoglobin, and hematocrit and, at the high doses, Heinz bodies) and into a 6-ml Vacutainer with no additives for determination of clinical chemistry.

Analysis of the LAP(I) feed was conducted as follows: Ten to twenty g of the feed was stirred in dichloromethane (100 ml) for 2 to 4 hours. This extracted solution was then filtered through an acid-washed Celite pad, with the flask and filter pad being rinsed three times with dichloromethane. The filtrate was passed through a chromatographic column containing $\approx$ 4 in. of 5% deactivated Florisil, topped with $\approx$ 1/2 in. of anhydrous sodium sulfate. The column was also washed with dichloromethane. This solution was evaporated to dryness and then redissolved in 3 ml of dichloromethane and 2 ml of methanol. The solution was then ready for quantitation via the external standard method.

Since the pink water residue consists of several components, RDX was chosen as a representative component and quantitation was therefore based on the amount of RDX present in the feeds. RDX was found to consist of 6% of the pink water residue; this was based on a w/w relationship. The actual contents in the feed samples, determined in this manner, were 0.22% for LAP, and 0.0028, 0.027, and 0.23%, respectively, for the low, mid, and high doses of LAP(I).

RESULTS

Observations

In general, the rats on the LAP(I) diets exhibited no visible signs of toxicity. One male at the 0.003% dose level appeared emaciated over the last 8 days of the study and a second male at the 0.03% level had that appearance on the last three days. The latter animal also had rales on two of those days. The weights of these animals at sacrifice were 212 and 165 g, respectively, well below the mean weights for these groups. Occasionally, rales or sneezing were observed in individual rats but the frequency of occurrence in the groups did not form a pattern that was treatment-related. One female at the 0.3% LAP(I) level died overnight on Day 8; its body was partially autolyzed when found.

One male in the untreated control group was found dead on Day 11 and was in a partially cannabilized and autolyzed state. This animal had had dyspnea on the two days preceding death. All positive control LAP rats had slightly discolored (red) urine beginning at the start of treatment and continuing throughout the study.

Body Weights

Tables 245 and 246 present weekly body weight data for the rats. Those fed the LAP diet had significantly lower body weights ($p < 0.01$; r test--B for males, A for females) than controls did throughout the 4-week test period. Males fed the diet containing 0.3% LAP(I) were also significantly lower in body weight than untreated controls, but not to the same degree as those treated with LAP; this observation is reinforced by the absence of any citation in the r-test for the LAP(I) rats. Females at the 0.3% LAP(I) level were also lower in body weight than controls, but not significantly so.

The mean body weights for LAP(I)-treated males at the lower doses also tend to be low, though not significantly, suggesting a dose response at these levels. There is a high degree of variance to these measurements, however, leading to a statistical citation in the Bartlett Chi-square column on Weeks 3 and 4. This increased variability results from the failure of one male in the 0.003% LAP(I) group to gain weight and from an actual weight loss by one male in the 0.03% group during this period (the same males noted above as appearing emaciated at the end of the treatment period). Since each male was paired in a cage with a second one that gained weight at or above the highest rate of any other in this group, consideration must be given to the possibility that the lower weight of these two rats results from male dominance by their partners rather than from the treatment. Consequently, the effect of LAP(I) treatment on body weight is clearly demonstrated only at the high dose.

Part 4

Tables 247 and 248 present weekly body weight differences for these rats. The calculations show a significantly low growth rate during the first week for both males and females at the 0.3% LAP(I) level, with resumption of a more normal growth pattern thereafter. Rats at the 0.3% LAP level lost substantial weight during the first week; thereafter, they increased their weights but, except for females during Week 4, at a slower rate than rats given the LAP(I) diet.

Food Consumption

Tables 249 through 252 present the weekly food consumption data for the rats on study. Food intake per animal (Tables 249 and 250) fed the 0.3% LAP(I) diet was lower at each recording than intake for controls (significantly so in half the cases). However, food intake calculated on a body weight basis (Tables 251 and 252) was significantly low during the first week only, recovering essentially to control levels within one to two weeks thereafter. These data parallel the observations made on body weight differences (Tables 247 and 248) and indicate that the rats at this LAP(I) level did not use their food as efficiently for growth during Week 1 as did the controls. In contrast, rats given the 0.3% LAP diet had the lowest food consumption of any group during Week 1 and consumption remained lower on almost every week thereafter.

Tables 253 and 254 provide the calculated doses of LAP(I) consumed weekly by the rats during this 4-week study.

Organ Weights

Tables 255 and 256 give the mean organ weights and organ-to-body and organ-to-brain weight ratios for the treated and control rats. The LAP rats had significantly lower kidney and heart weights and organ-to-brain weight ratios. Several organ-to-body weight ratios were significantly high due to the low body weights for these rats. The liver-to-brain weight ratio was significantly low for the males but not for the females. These effects on heart and kidney but not liver were also observed in rats treated for 13 weeks with 0.5% LAP (Tables 219 and 220).

In contrast, no alterations were seen in any parameter for LAP(I)-treated groups that might be attributed to the treatment. The brain-to-body weight ratio for males did increase as dose was increased, but this change was undoubtedly due to a corresponding decrease in body weights for these groups and not to an effect of treatment on the brain. The testes-to-body weight ratio was also slightly higher than the control ratio for the same reason.

Hematology

Tables 257 and 258 present hematological determinations on the rats at sacrifice. As before (Tables 221 and 222), LAP increased MCV and decreased RBC, Hgb, and Hct; other microdeterminations were not significantly altered. Percent PMN was lower and percent lymphocytes was higher in these blood specimens (significantly for males) than in untreated controls. Rats treated with 0.3% LAP also had slightly elevated percent of reticulocytes (statistically significant for females).

For LAP(I) rats at the 0.3% dose level, RBC, Hgb, and Hct were lowered but not to the same extent as for LAP, and only Hct for males and Hgb for females were cited statistically. The only other citation at this level was the low percent of PMN for females, but both the percentage and the total counts were within the normal range. WBC for males at the 0.3% level was high compared with the value for untreated controls, but neither abnormally nor significantly so. Alterations cited in other groups [e.g., percent of atypical lymphocytes for males and percent eosinophils for females at the 0.003% LAP(I) level] were attributed to variations in these particular groups and not to the treatment.

Clinical Chemistry

Tables 259 and 260 give the clinical chemistry on the sera of the rats at sacrifice. As expected, the LAP rats exhibited high cholesterol levels ($p < 0.01$). Among other changes noted were significantly high albumin and low glucose in females and significantly high SGOT in males ($p < 0.05$ for each parameter). In contrast, LAP(I) was without any significant effect on the clinical chemistry.

Histopathology

Tissues from all rats in each group were examined microscopically. The results are summarized in Tables 261 and 262. Noticeable though slight foci of lymphocytes occurred with greater frequency in the livers of males at the 0.3% LAP(I) level and of females at both the 0.03 and 0.3% levels than in other groups. This may possibly reflect a response to the treatment.

Leukocytes were present in the tracheal lumen of five males at the 0.3% level and of three males at the 0.003% level; no females were thus affected, however. Almost all the animals with this response also had tracheitis, a common observation in rats; since all groups, including controls, were similarly affected, an association of these leukocytic deposits with the treatment is obscure. Chronic respiratory disease was prevalent in all groups to approximately the same extent (50 to 80% of the rats in each group); this observation therefore was not treatment-related.

Part 4

In regard to the rats treated with LAP, seven of the males and eight of the females had hemosiderosis of the spleen after 4 weeks of treatment. This condition, also found in the earlier study (Part 3), was attributable to the treatment. Uterine hypoplasia was not observed in the LAP females, as it was when females were treated for 13 weeks with 0.5% LAP in their diets (Part 3).

DISCUSSION AND CONCLUSIONS

Ten male and ten female rats each were treated with 0.003, 0.03, and 0.3% LAP(I) in the diet for four consecutive weeks. The toxic symptoms observed were compared with those exhibited by 10 male and 10 female rats concurrently treated with 0.3% LAP in the diet. The LAP(I) treatment produced few toxic signs, even at the highest dose. RBC, Hgb, and Hct were lower in males and females than in untreated controls, occasionally significantly so, suggesting the presence of a very mild anemia. Lymphocytic foci were observed in the livers of several of the rats in the high dose groups at an appreciably higher frequency than in other groups; this lesion may be treatment-related. The increase in lymphocyte count (WBC x % lymphocytes) at the high dose, though marginal, may be related to this observation. No alterations were noted in organ weights, other cell differentials, or clinical chemistry. However, body weights were lower than in controls in an apparently dose-related manner (Tables 245 and 246). Food intake and food efficiency for the high dose LAP(I) rats were temporarily (first week only) lower also. The fairly prompt recovery in food intake and body weight gain in rats at the high-dose level after the first week indicates that the temporary suppression in weight gain may have been substantially due to an aversion to the diet and not to the inherent toxicity of the irradiated mixture. No toxic signs were recorded in the daily observations.

Rats treated with 0.3% LAP, on the other hand, had significantly lower body weights, weight gain, and food intake; smaller kidneys and hearts; a mild anemia; elevated serum cholesterol; hemosiderosis of the spleen; and discolored urine. All of these observations were made earlier on rats treated with 0.5% LAP for 13 weeks (Part 3). Several findings made on rats at the 0.5% level (e.g., uterine hypoplasia, testicular atrophy, elevated bilirubin and BUN) either were not observed at the 0.3% level or were not significantly altered. Whether this was due to the lower dose or to the length of treatment could not be established from the data.

In comparing the results on the test mixtures at the 0.3% level, it is clear from the presence of a number of toxic signs in the LAP rats and the virtual absence of signs in the LAP(I) rats that, based on the parameters measured, the irradiated mixture is less toxic than

the unirradiated mixture upon repeated oral administration for up to 4 weeks. These findings contrast with those obtained in the mouse (acute oral LD50s), in which the irradiated mixture was more toxic, but agree with results from aquatic testing.[17] We consider that a repeated-exposure test is more relevant to the environmental situation.

TABLE 245

EFFECTS OF LAP(I) ON BODY WEIGHTS (G)
OF MALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET	T R
INITIAL		154.80 ± 4.36 (10)	158.60 ± 3.04 (10)		157.00 ± 3.79 (10)		154.90 ± 4.00 (10)		155.60 ± 4.51 (10)	
WEEK 1		199.50 ± 11.1 (10)	139.10 ± 4.63 (10)	+ B	206.20 ± 7.08 (10)		198.60 ± 8.17 (10)		174.20 ± 5.12 (10)	
WEEK 2		255.33 ± 4.80 (9)	158.80 ± 6.55 (10)	+ B	254.00 ± 9.47 (10)		247.50 ± 10.6 (10)		215.60 ± 5.34 (10)	*
WEEK 3	*	293.33 ± 6.29 (9)	183.60 ± 5.79 (10)	+ B	282.10 ± 12.5 (10)		284.90 ± 12.7 (10)		259.90 ± 4.55 (10)	+
WEEK 4	+	323.22 ± 6.52 (9)	211.10 ± 7.10 (10)	+ B	316.90 ± 13.8 (10)		309.00 ± 19.0 (10)		293.10 ± 4.57 (10)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A,
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - x .
† 0.3 LAP (IN DIET)

TABLE 246

EFFECTS OF LAP(I) ON BODY WEIGHTS (G)
OF FEMALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET	T R
INITIAL		147.00 ± 4.42 (10)	146.60 ± 4.27 (10)		146.90 ± 4.61 (10)		144.80 ± 3.38 (10)		144.50 ± 3.42 (10)	
WEEK 1		168.60 ± 3.65 (10)	136.50 ± 4.02 (10)	+ A	174.90 ± 2.86 (10)		168.80 ± 4.07 (10)		154.60 ± 3.09 (10)	
WEEK 2		189.80 ± 3.91 (10)	142.10 ± 5.24 (10)	+ A	197.60 ± 3.12 (10)		190.50 ± 3.67 (10)		172.56 ± 3.15 (9)	
WEEK 3		202.50 ± 4.40 (10)	155.30 ± 5.61 (10)	+ A	212.50 ± 4.08 (10)		202.90 ± 4.09 (10)		184.67 ± 4.32 (9)	
WEEK 4		212.50 ± 3.88 (10)	165.60 ± 5.93 (10)	+ A	223.00 ± 4.01 (10)		214.70 ± 4.59 (10)		195.78 ± [illegible] (9)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A, 20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - x .
† 0.3 LAP (IN DIET)

TABLE 247

EFFECTS OF LAP(I) ON DIFFERENCES IN BODY WEIGHTS (G)
OF MALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET
WEEK 1		44.70 ± 7.22 (10)	-19.50 ± 3.11 (10)	+ D	49.20 ± 5.00 (10)		43.70 ± 7.08 (10)		18.60 ± 3.56
WEEK 2	+	45.78 ± 2.39 (9)	19.70 ± 2.93 (10)	+ C	47.80 ± 6.48 (10)		48.90 ± 3.03 (10)		41.40 ± 1.77
WEEK 3	*	38.00 ± 2.64 (9)	24.80 ± 1.85 (10)	+ A	28.10 ± 4.74 (10)		37.40 ± 3.8[illegible] (10)		44.30 ± 1.37
WEEK 4	+	29.89 ± 3.19 (9)	27.50 ± 2.32 (10)		34.80 ± 2.62 (10)		24.10 ± 6.82 (10)		33.20 ± 1.47

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A,
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - x .
† 0.3 LAP (IN DIET)

TABLE 248

EFFECTS OF LAP(I) ON DIFFERENCES IN BODY WEIGHTS (G)
OF FEMALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET	T R
WEEK 1		21.60 ± 2.88 (10)	-10.10 ± 1.31 (10)	+ D	28.00 ± 2.18 (10)		24.00 ± 3.07 (10)		10.10 ± 1.61 (10)	* B
WEEK 2		21.20 ± 1.47 (10)	5.60 ± 1.73 (10)	+ D	22.70 ± 1.67 (10)		21.70 ± 2.17 (10)		19.00 ± 3.04 (9)	
WEEK 3		12.70 ± 1.78 (10)	11.20 ± 1.09 (10)		14.90 ± 1.31 (10)		12.40 ± 1.24 (10)		12.11 ± 1.42 (9)	
WEEK 4		10.00 ± 1.47 (10)	12.30 ± 1.00 (10)		10.50 ± 1.02 (10)		11.80 ± 1.19 (10)		11.11 ± .790 (9)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A, 20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - x .
† 0.3 LAP (IN DIET)

TABLE 249

EFFECTS OF LAP(I) ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF MALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	POSITIVE CONTROL†	TREATMENT GROUPS .C03 % IN DIET	W	.03 % IN DIET	W	0.3 % IN DIET
WEEK 1	17.8 ± 1.20 (4)	5.9 ± .588 (4)	18.3 ± 1.01 (4)		17.0 ± 1.34 (4)		10.7 ± 1.05
WEEK 2	28.7 ± 3.38 (4)	13.7 ± 1.02 (4)	22.4 ± 1.51 (4)		23.8 ± 1.12 (4)		20.2 ± .764
WEEK 3	25.4 ± 1.15 (4)	15.3 ± .324 (4)	24.0 ± .702 (4)		24.8 ± 1.42 (4)		21.7 ± .503
WEEK 4	27.1 ± 2.50 (4)	15.9 ± .327 (4)	24.4 ± 1.67 (4)		23.2 ± 2.21 (4)		22.7 ± .517

ENTRIES ARE MEANS AND STANDARD ERRORS WITH CAGE N IN PARENTHESES
W IS A WILLIAMS TEST OF THE LOWEST DOSE SIGNIFICANTLY DIFFERENT FROM CONTROL
CONFIDENCE LEVEL = .95
† 0.3 % LAP (IN DIET)

TABLE 250

EFFECTS OF LAP(I) ON FOOD CONSUMPTION (G/ANIMAL/DAY)
OF FEMALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	POSITIVE CONTROL†	TREATMENT GROUPS: .003 % IN DIET	W	.03 % IN DIET	W	0.3 % IN DIET	W
WEEK 1	15.3 ± .396 (4)	5.4 ± .424 (4)	15.4 ± .358 (4)		14.2 ± .998 (4)		11.0 ± .799 (4)	*
WEEK 2	15.4 ± .384 (4)	10.5 ± .639 (4)	16.9 ± .596 (4)		16.3 ± .827 (4)		14.5 ± .404 (4)	
WEEK 3	16.9 ± .482 (4)	11.0 ± .638 (4)	17.7 ± .819 (4)		16.2 ± .672 (4)		15.1 ± .342 (4)	
WEEK 4	17.9 ± .610 (4)	12.1 ± .297 (4)	17.9 ± .952 (4)		16.1 ± .454 (4)		15.1 ± .432 (4)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH CAGE N IN PARENTHESES
W IS A WILLIAMS TEST OF THE LOWEST DOSE SIGNIFICANTLY DIFFERENT FROM CONTROL
* CONFIDENCE LEVEL = .95
† 0.3 % LAP (IN DIET)

TABLE 251

EFFECTS OF LAP(I) ON FOOD CONSUMPTION (G/KG (BODY WT)-DAY)
OF MALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	POSITIVE CONTROL†	TREATMENT GROUPS .003 % IN DIET	W	.03 % IN DIET	W	0.3 % IN DIET
WEEK 1	89.2 ± 3.08 (4)	42.4 ± 2.99 (4)	88.5 ± 1.89 (4)		85.5 ± 2.64 (4)		62.2 ± 7.28
WEEK 2	113.1 ± 15.5 (4)	86.7 ± 7.01 (4)	88.1 ± 4.97 (4)		96.1 ± 1.82 (4)		93.4 ± 1.78
WEEK 3	86.5 ± 2.29 (4)	83.9 ± 3.98 (4)	85.1 ± 1.34 (4)		86.9 ± 1.60 (4)		83.4 ± 1.21
WEEK 4	83.8 ± 6.61 (4)	75.0 ± 2.61 (4)	76.5 ± 4.51 (4)		74.8 ± 2.76 (4)		77.5 ± 2.67

ENTRIES ARE MEANS AND STANDARD ERRORS WITH CAGE N IN PARENTHESES
W IS A WILLIAMS TEST OF THE LOWEST DOSE SIGNIFICANTLY DIFFERENT FROM CONTROL
* CONFIDENCE LEVEL = .95
† 0.3 % LAP (IN DIET)

TABLE 252

EFFECTS OF LAP(I) ON FOOD CONSUMPTION (G/KG (BODY WT)-DAY)
OF FEMALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	CONTROL GROUP	POSITIVE CONTROL†	TREATMENT GROUPS: .003 % IN DIET	W	TREATMENT GROUPS: .03 % IN DIET	W	TREATMENT GROUPS: 0.3 % IN DIET	W
WEEK 1	90.5 ± 1.25 (4)	39.4 ± 1.74 (4)	88.0 ± 2.68 (4)		84.2 ± 4.35 (4)		71.4 ± 6.01 (4)	*
WEEK 2	81.3 ± 1.79 (4)	74.6 ± 5.09 (4)	85.4 ± 2.99 (4)		85.6 ± 3.10 (4)		84.2 ± 2.11 (4)	
WEEK 3	83.3 ± 1.16 (4)	72.0 ± .826 (4)	83.4 ± 2.52 (4)		79.6 ± 2.07 (4)		81.8 ± 1.50 (4)	
WEEK 4	84.3 ± 2.26 (4)	72.8 ± 2.00 (4)	79.9 ± 3.74 (4)		74.5 ± .976 (4)		77.0 ± 2.53 (4)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH CAGE N IN PARENTHESES
W IS A WILLIAMS TEST OF THE LOWEST DOSE SIGNIFICANTLY DIFFERENT FROM CONTROL
* CONFIDENCE LEVEL = .95
† 0.3 % LAP (IN DIET)

TABLE 253

DOSES OF LAP(I) (MG/KG (BODY WT)-DAY) IN DIETS CONSUMED BY MALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS: POSITIVE CONTROL†	.003 % IN DIET	.03 % IN DIET	0.3 % IN DIET
WEEK 1	127 15	2.66	25.6	186.5
WEEK 2	259.96	2.64	28.8	286.3
WEEK 3	251.83	2.55	26.1	250.2
WEEK 4	225.01	2.30	22.4	232.4

† 0.3 % LAP (IN DIET)

TABLE 254

DOSES OF LAP(I) (MG/KG (BODY WT)-DAY) IN DIETS CONSUMED BY FEMALE RATS DURING 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	TREATMENT GROUPS			
	POSITIVE CONTROL†	.003 % IN DIET	.03 % IN DIET	0.3 % IN DIET
WEEK 1	118.27	2.64	25.2	214.3
WEEK 2	223.89	2.56	25.7	252.6
WEEK 3	216.10	2.50	23.9	245.3
WEEK 4	218.55	2.40	22.4	231.0

† 0.3 % LAP (IN DIET)

TABLE 255

EFFECTS OF LAP(I) ON ORGAN WEIGHTS (G)
ORGAN-TO-BODY WEIGHT PATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF MALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET	T R
FINAL WEIGHT	+	297.89 ± 6.35 (9)	190.60 ± 6.29 (10)	+ B	288.20 ± 13.5 (10)		284.60 ± 17.5 (10)		269.30 ± 4.50 (10)	*
BRAIN		1.98 ± .044 (9)	1.95 ± .040 (10)		2.01 ± .031 (10)		2.04 ± .033 (10)		2.05 ± .032 (10)	
HEART		1.20 ± .051 (9)	.84 ± .048 (10)	+ B	1.14 ± .040 (10)		1.20 ± .057 (10)		1.09 ± .046 (10)	
LIVER		10.11 ± .420 (9)	8.76 ± .395 (10)		9.81 ± .558 (10)		9.94 ± .511 (10)		9.82 ± .226 (10)	
SPLEEN		.69 ± .026 (9)	.62 ± .027 (10)	A	.62 ± .031 (10)	A	.60 ± .036 (10)	A	.58 ± .024 (10)	A
KIDNEYS		2.53 ± .155 (9)	1.73 ± .071 (10)	+ B	2.54 ± .132 (10)		2.48 ± .127 (10)		2.40 ± .085 (10)	
TESTES		3.03 ± .083 (9)	2.74 ± .126 (10)		2.96 ± .087 (10)		2.88 ± .090 (10)		2.96 ± .068 (10)	
BRAIN/BODY	+	6.66 ± .149 (9)	10.27 ± .210 (10)	+ C	7.14 ± .431 (10)		7.47 ± .543 (10)		7.62 ± .165 (10)	+
HEART/BODY		4.04 ± .159 (9)	4.44 ± .219 (10)		4.01 ± .141 (10)		4.37 ± .278 (10)		4.03 ± .161 (10)	
LIVER/BODY		33.84 ± .817 (9)	45.86 ± .864 (10)	+ B	33.97 ± .743 (10)		3[illegible].96 ± .448 (10)		36.44 ± .765 (10)	
SPLEEN/BODY		2.31 ± .072 (9)	3.25 ± .134 (10)	+ B	2.17 ± .100 (10)		2.13 ± .103 (10)		2.16 ± .091 (10)	
KIDNEYS/BODY		8.44 ± .366 (9)	9.05 ± .236 (10)		8.82 ± .184 (10)		8.83 ± .298 (10)		8.93 ± .357 (10)	
TESTES/BODY	*	10.20 ± .245 (9)	14.42 ± .579 (10)	+ B	10.51 ± .665 (10)		10.50 ± .753 (10)		10.98 ± .280 (10)	*
HEART/BRAIN		.61 ± .023 (9)	.43 ± .021 (10)	+ B	.57 ± .018 (10)		.58 ± .023 (10)		.53 ± .017 (10)	A
LIVER/BRAIN	*	5.11 ± .181 (9)	4.49 ± .149 (10)	*	4.91 ± .297 (10)		4.84 ± .262 (10)		4.80 ± .121 (10)	
SPLEEN/BRAIN		.35 ± .013 (9)	.32 ± .014 (10)		.31 ± .016 (10)	A	.29 ± .016 (10)	A	.29 ± .013 (10)	A
KIDNEYS/BRAIN	*	1.28 ± .079 (9)	.88 ± .024 (10)	+ B	1.27 ± .075 (10)		1.21 ± .054 (10)		1.[illegible]7 ± .040 (10)	
TESTES/BRAIN		1.54 ± .047 (9)	1.41 ± .062 (10)		1.47 ± .041 (10)		1.41 ± .044 (10)		1.44 ± .022 (10)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A,
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - x .
† 0.3 LAP (IN DIET)

TABLE 256

EFFECTS OF LAP(I) ON ORGAN WEIGHTS (G)
ORGAN-TO-BODY WEIGHT RATIOS (1000XG/G) AND ORGAN-TO-BRAIN WEIGHT RATIOS (G/G)
OF FEMALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET	T R
FINAL WEIGHT		202.50 ± 4.26 (10)	152.30 ± 6.04 (10)	+ A	213.80 ± 4.33 (10)		204.10 ± 3.80 (10)		182.70 ± 4.77 (10)	
BRAIN		1.88 ± .022 (10)	1.90 ± .033 (10)		1.94 ± .034 (10)		1.87 ± .040 (10)		1.90 ± .032 (9)	
HEART		.94 ± .046 (10)	.70 ± .041 (10)	+ A	.89 ± .044 (10)		.90 ± .032 (10)		.84 ± .034 (9)	
LIVER		6.52 ± .294 (10)	7.03 ± .293 (10)		6.94 ± .268 (10)		6.35 ± .155 (10)		6.54 ± .173 (9)	
SPLEEN		.48 ± .025 (10)	.51 ± .020 (10)		.54 ± .022 (10)	A	.55 ± .031 (10)	A	.50 ± .026 (9)	
KIDNEYS		1.62 ± .058 (10)	1.38 ± .058 (10)	*	1.66 ± .039 (10)		1.59 ± .044 (10)		1.61 ± .045 (9)	
BRAIN/BODY		9.29 ± .158 (10)	12.60 ± .359 (10)	+ B	9.09 ± .168 (10)		9.16 ± .175 (10)		[illegible].35 ± .233 (9)	
HEART/BODY		4.63 ± .211 (10)	4.58 ± .177 (10)		4.18 ± .186 (10)		4.42 ± .178 (10)		[illegible].57 ± .126 (9)	
LIVER/BODY		32.18 ± 1.19 (10)	46.19 ± .943 (10)	+ B	32.38 ± .844 (10)		31.13 ± .582 (10)		35.59 ± 1.17 (9)	
SPLEEN/BODY		2.36 ± .101 (10)	3.40 ± .154 (10)	+ B	2.50 ± .075 (10)		2.72 ± .166 (10)		2.71 ± .131 (9)	
KIDNEYS/BODY		7.97 ± .203 (10)	9.08 ± .150 (10)	+	7.76 ± .141 (10)		7.80 ± .208 (10)		8.72 ± .165 (9)	
HEART/BRAIN		.50 ± .023 (10)	.37 ± .016 (10)	+ B	.46 ± .021 (10)		.48 ± .015 (10)		.44 ± .014 (9)	A
LIVER/BRAIN		3.48 ± .170 (10)	3.69 ± .110 (10)		3.57 ± .124 (10)		3.41 ± .113 (10)		3.45 ± .120 (9)	
SPLEEN/BRAIN		.26 ± .013 (10)	.27 ± .009 (10)		.28 ± .010 (10)		.30 ± .018 (10)	A	.26 ± .014 (9)	
KIDNEYS/BRAIN		.86 ± .028 (10)	.73 ± .023 (10)	* A	.86 ± .020 (10)		.85 ± .029 (10)		.85 ± .025 (9)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A,
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - π .
† 0.3 LAP (IN DIET)

TABLE 257

EFFECTS OF LAP(1) ON HEMATOLOGY
OF MALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET	T R
RBC (X 10^6)		7.84 ± .258 (8)	6.15 ± .147 (8)	+ A	7.36 ± .271 (8)		7.69 ± .326 (7)		7.21 ± .157 (10)	
HGB (G %)		15.43 ± .207 (8)	13.51 ± .242 (8)	+	15.02 ± .192 (8)		15.53 ± .545 (7)		14.23 ± .270 (10)	
HCT (%)		44.50 ± .945 (8)	39.25 ± .675 (8)	*	43.62 ± 1.15 (8)		43.14 ± 1.65 (7)		39.80 ± .892 (10)	*
MCV $(U)^3$	*	57.62 ± .800 (8)	64.87 ± 1.42 (8)	+	60.12 ± 1.25 (8)		57.14 ± .404 (7)		55.90 ± .526 (10)	
MCH (MUG)		19.75 ± .597 (8)	22.00 ± .499 (8)		20.70 ± .681 (8)		20.40 ± .446 (7)		19.66 ± .198 (10)	
MCHC (%)		34.54 ± .701 (8)	34.41 ± .700 (8)		34.81 ± .840 (8)		36.14 ± .716 (7)		35.71 ± .424 (10)	
WBC (X 10^3)		9.48 ± .941 (8)	7.99 ± 1.10 (8)		6.28 ± .731 (8)		8.22 ± .998 (7)		11.94 ± 1.17 (10)	
PMN (%)	+	17.75 ± 1.83 (8)	11.12 ± 1.22 (8)	* A	19.38 ± 2.73 (8)		23.57 ± 7.09 (7)		14.80 ± 3.08 (10)	
BANDS (%)		.13 ± .125 (8)	0.00 ± 0.00 (8)	x	.13 ± .125 (8)		.14 ± .143 (7)	x	.10 ± .100 (10)	x
LYMPH (%)	*	77.87 ± 2.16 (8)	83.75 ± 1.52 (8)	*	71.12 ± 2.72 (8)		68.43 ± 6.54 (7)		78.60 ± 3.75 (10)	
ATYP LYMPH(%)	*	2.25 ± .250 (8)	1.75 ± .313 (8)		5.63 ± .460 (8)	+ D	3.86 ± 1.06 (7)		2.60 ± .653 (10)	
MONO (%)		1.38 ± .375 (8)	2.63 ± .730 (8)	x	3.38 ± .730 (8)	x	3.14 ± .769 (7)	x	2.60 ± .884 (10)	x
EOSIN (%)		.63 ± .263 (8)	.75 ± .366 (8)		.25 ± .250 (8)		.86 ± .261 (7)		1.10 ± .277 (10)	
BASO (%)		0.00 ± 0.00 (8)	0.00 ± 0.00 (8)	x	.13 ± .125 (8)	x	0.00 ± 0.00 (7)	x	.10 ± .100 (10)	
RETICS (%)		.31 ± .195 (8)	.59 ± .195 (8)		.43 ± .123 (5)		.57 ± .165 (4)		.39 ± .092 (10)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A, 20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - x .
† 0.3 LAP (IN DIET)

TABLE 259

EFFECTS OF LAP(I) ON HEMATOLOGY
OF FEMALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS: .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET	T R
RBC (X 10⁶)		7.51 ± .196 (10)	6.31 ± .159 (9)	+ A	7.40 ± .191 (10)		7.42 ± .087 (10)		7.13 ± .116 (7)	
HGB (G %)		15.55 ± .148 (10)	13.76 ± .231 (9)	+	14.73 ± .180 (10)		15.11 ± .205 (10)		14.49 ± .200 (7)	*
HCT (%)		41.80 ± .772 (10)	38.22 ± .547 (9)	*	40.80 ± 1.08 (10)		41.10 ± .605 (10)		39.00 ± .577 (7)	
MCV (U)3		55.90 ± .482 (10)	61.11 ± .716 (9)	+	56.00 ± .422 (10)		56.20 ± .416 (10)		55.29 ± .360 (7)	
MCH (UUG)	*	20.80 ± .611 (10)	21.89 ± .309 (9)		19.70 ± .367 (10)		20.50 ± .167 (10)		20.29 ± .286 (7)	
MCHC (%)		37.54 ± .510 (10)	36.44 ± .475 (9)		36.10 ± .640 (10)		37.10 ± .348 (10)		37.71 ± .360 (7)	
WBC (X 10³)		6.75 ± .649 (10)	9.64 ± 1.34 (9)		7.15 ± .723 (10)		7.57 ± 1.12 (10)		8.45 ± .730 (7)	
PMN (%)		19.50 ± 1.58 (10)	14.11 ± 1.49 (9)		17.40 ± 1.50 (10)		16.20 ± 1.52 (10)		11.14 ± 2.39 (7)	* B
BANDS (%)		0.00 ± 0.00 (10)	0.00 ± 0.00 (9)	x	.20 ± .133 (10)	x	.10 ± .100 (10)	x	0.00 ± 0.00 (7)	B
LYMPH (%)		77.10 ± 1.42 (10)	82.22 ± 1.52 (9)		77.50 ± 1.86 (10)		78.40 ± 1.59 (10)		84.43 ± 1.96 (7)	
ATYP LYMPH(%)		1.80 ± .359 (10)	2.44 ± .503 (9)		2.20 ± .291 (10)		2.30 ± .300 (10)		2.43 ± .369 (7)	
MONO (%)		1.30 ± .495 (10)	.78 ± .434 (9)		1.20 ± .663 (10)		1.70 ± .473 (10)		1.29 ± .565 (7)	
EOSIN (%)		.30 ± .153 (10)	.33 ± .167 (9)	x	1.50 ± .342 (10)	* x	1.00 ± .258 (10)	x	.71 ± .184 (7)	x
BASO (%)		0.00 ± 0.00 (10)	0.00 ± 0.00 (9)		0.00 ± 0.00 (10)		0.00 ± 0.00 (10)		0.00 ± 0.00 (7)	
RETICS (%)	+	.44 ± .112 (10)	1.19 ± .265 (9)	*			.19 ± .038 (5)	* B	.33 ± .104 (7)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A,
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - x .
† 0.3 LAP (IN DIET)

TABLE 259

EFFECTS OF LAP(I) ON CLINICAL CHEMISTRY
OF MALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET	T R
ALBUMIN (GM%)		4.88 ± .146 (9)	5.04 ± .150 (9)		4.37 ± .178 (10)		4.80 ± .114 (10)		4.59 ± .121 (10)	
BILI (MG %)		.17 ± .035 (4)	.22 ± .013 (4)	B	.18 ± .023 (5)		.17 ± .020 (6)		.22 ± .030 (6)	B
BUN (MG %)		14.99 ± 1.12 (9)	17.11 ± .949 (9)		15.30 ± .746 (10)		14.90 ± 1.17 (10)		15.30 ± .731 (10)	
CHOL (MG %)		30.11 ± 2.39 (9)	50.11 ± 3.83 (9)	+ B	28.90 ± 3.31 (10)		33.40 ± 2.10 (10)		34.20 ± 2.73 (10)	
CREAT (MG %)		.42 ± .022 (9)	.38 ± .022 (9)	A	.39 ± .028 (10)		.39 ± .018 (10)		.40 ± .026 (10)	
GLUCOSE (MG%)		145.67 ± 7.47 (9)	133.22 ± 10.2 (9)		123.20 ± 8.79 (10)		138.90 ± 7.32 (10)		140.30 ± 8.34 (10)	
P (MG %)	*	5.60 ± .384 (9)	7.11 ± .334 (9)		6.45 ± .245 (10)		5.72 ± .295 (10)		6.36 ± .645 (10)	
LDH (IU/L)	*	218.11 ± 35.3 (9)	286.67 ± 52.1 (9)		215.80 ± 39.7 (10)		237.20 ± 35.8 (10)		379.80 ± 86.6 (10)	
TRIG (MG %)		47.56 ± 3.13 (9)	55.44 ± 6.11 (9)		52.10 ± 5.73 (10)		61.90 ± 5.85 (10)		70.70 ± 8.12 (10)	
URIC ACID(MG%)	+	1.37 ± .112 (9)	2.37 ± .535 (9)		1.43 ± .106 (10)		1.22 ± .192 (10)		1.79 ± .216 (10)	
PROTEIN (MG%)		6.93 ± .189 (9)	7.02 ± .215 (9)		6.59 ± .173 (10)		6.96 ± .238 (10)		6.69 ± .194 (10)	
SGPT (IU/L)	+	29.22 ± 2.40 (9)	35.33 ± 7.76 (9)		28.70 ± 2.48 (10)		35.30 ± 2.43 (10)		27.40 ± 3.03 (10)	
SGOT (IU/L)	+	92.00 ± 5.99 (9)	146.00 ± 21.7 (9)	*	89.40 ± 7.41 (10)		94.20 ± 7.90 (10)		106.60 ± 14.2 (10)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A, 20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - x .
† 0.3 LAP (IN DIET)

TABLE 260

EFFECTS OF LAP(I) ON CLINICAL CHEMISTRY
OF FEMALE RATS AFTER 4 WEEKS OF TREATMENT

DEPENDENT VARIABLE	B C	CONTROL GROUP	POSITIVE CONTROL†	T R	TREATMENT GROUPS .003 % IN DIET	T R	.03 % IN DIET	T R	0.3 % IN DIET	T R
ALBUMIN (GM%)		4.38 ± .149 (10)	5.25 ± .167 (6)	*	4.49 ± .124 (9)		4.40 ± .208 (10)		4.38 ± .202 (8)	
BILI (MG %)		.22 ± .036 (10)	.27 ± .042 (6)		.22 ± .036 (9)		.26 ± .037 (10)		.25 ± .030 (8)	
BUN (MG %)		16.40 ± 1.67 (10)	21.00 ± 1.26 (6)		16.89 ± .841 (9)		18.30 ± 1.02 (10)		16.50 ± .982 (8)	
CHOL (MG %)		46.30 ± 3.87 (10)	85.17 ± 6.10 (6)	+ C	49.11 ± 4.07 (9)		46.00 ± 4.22 (10)		59.62 ± 5.48 (8)	
CREAT (MG %)		.51 ± .038 (10)	.45 ± .034 (6)		.47 ± .029 (9)		.43 ± .033 (10)		.45 ± .033 (8)	
GLUCOSE (MG%)	*	154.30 ± 8.54 (10)	130.17 ± 3.11 (6)	*	140.00 ± 13.9 (9)		134.10 ± 8.13 (10)		133.50 ± 5.87 (8)	
P (MG %)		6.57 ± .691 (10)	7.58 ± 1.15 (6)		6.71 ± .586 (9)		7.31 ± .800 (9)		7.99 ± 1.13 (8)	
LDH (IU/L)	+	228.20 ± 30.4 (10)	299.83 ± 50.9 (6)		169.11 ± 5.19 (9)		203.40 ± 36.3 (10)		260.50 ± 89.8 (8)	
TRIG (MG %)	*	42.10 ± 4.02 (10)	43.50 ± 4.28 (6)		40.33 ± 7.70 (9)		34.70 ± 2.31 (10)		49.87 ± 7.09 (8)	
URIC ACID(MG%)	+	2.24 ± .475 (10)	1.27 ± .369 (6)		1.73 ± .606 (9)		1.90 ± .917 (10)		1.39 ± .466 (8)	
PROTEIN (MG %)		6.29 ± .269 (10)	7.30 ± .179 (6)		6.30 ± .129 (9)		7.15 ± .329 (10)		7.21 ± .305 (8)	
SGPT (IU/L)	*	26.80 ± 1.80 (10)	26.17 ± 4.50 (6)		31.11 ± 4.54 (9)		23.20 ± 1.78 (10)		23.50 ± 1.21 (8)	
SGOT (IU/L)	*	95.20 ± 6.70 (10)	102.33 ± 8.87 (6)		94.44 ± 10.2 (9)		81.90 ± 7.79 (10)		96.62 ± 20.2 (8)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
\+ CONFIDENCE LEVEL = .99
B = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 % - A,
20 % - B, 35 % - C, 50 % - D. RATIO TEST CANNOT BE CALCULATED - x .
† 0.3 LAP (IN DIET)

Table 261

MICROSCOPIC LESIONS IN MALE RATS AFTER 4 WEEKS OF LAP(I) TREATMENT

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.3%*	0.003%	0.03%	0.3%
	Group Designation				
	D0	D1	D2	D3	D4
	Animal Number				
Cecum					
Calcification, focal mucosal	106,109		125	135	143
Epididymus					
Aspermia			128	136	
Kidneys					
Hydronephrosis				131	143
Hydronephrosis and nephrosis, focal			123,127	140	141,145,146
Lymphocytic foci					
Lymphocytic foci and cortical tubular regeneration	107				
Nephrosis, focal	104		121	135	
Cortical tubular regeneration	105				149
Liver					
Lymphocytic foci	107,109	111,116,117	123,126	137,139	142,145,147 149,150
Polymorphonuclear foci	105				
Lung					
Abcesses; changed aeration pattern; respiratory disease, chronic;	102				
Abcesses; changed aeration pattern; respiratory disease, chronic; bronchitis, chronic purulent	103				
Changed aeration pattern and chronic respiratory disease	105,106,107 108,109,110	111,113,118 119,120	123,126,127 128,129,130	132,133,134 135,136,138 139,140	143,146,148 149,150

* [illegible]tive [illegible]ntr[illegible] LAP[illegible]

Table 261

MICROSCOPIC LESIONS IN MALE RATS AFTER 4 WEEKS OF LAP(I) TREATMENT

(Continued)

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.3%*	0.003%	0.03%	0.3%
	Group Designation				
	D0	D1	D2	D3	D4
	Animal Number				
Lung					
Changed aeration pattern; bronchiectasis, chronic purulent and chronic respiratory disease		112,114,117	121	131	141,142
Changed aeration pattern; hemorrhage and chronic respiratory disease	104	115	122,125		144,145,147
Changed aeration pattern; hemorrhage; bronchiectasis, chronic purulent and chronic respiratory disease			124		
Bronchiectasis, chronic purulent and chronic respiratory disease				137	
Chronic respiratory disease		116			
Lymph nodes					
Hemorrhage, focal				139	
Pituitary					
Chromophobe adenoma			130		
Prostate					
Prostatitis, chronic			128		
Spleen					
Hemosiderosis		111,113,115 116,117,118 120			
Testes					
Atrophy			128	136	
Thymus					
Hemorrhage					148

* Positive control (LAP).

Table 261

MICROSCOPIC LESIONS IN MALE RATS AFTER 4 WEEKS OF LAP(I) TREATMENT

(Concluded)

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.3%*	0.003%	0.03%	0.3%
	Group Designation				
	D0	D1	D2	D3	D4
	Animal Number				
Trachea					
Leukocytes in the lumen			122	137	144
Leukocytes in the lumen; chronic tracheitis, focal			128,129		141,142,147 148
Acute tracheitis, mild, focal; chronic tracheitis, focal	108				
Chronic tracheitis, focal	102,107,110	111,116	123,125,126	131,135,139 140	143

* Positive control (LAP)

Table 262

MICROSCOPIC LESIONS IN FEMALE RATS AFTER 4 WEEKS OF LAP(I) TREATMENT

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.3%*	0.003%	0.03%	0.3%
	Group Designation				
	D0	D1	D2	D3	D4
	Animal Number				
Colon					
Enlarged and dilated			227		
Eye					
Absence of rods and cones	205				
Kidneys					
Hydronephrosis, marked	208				
Lymphocytic foci			222		
Lymphocytic foci and cortical tubular regeneration					243
Nephrocalcinosis, slight focal		211		233	248
Cortical tubular regeneration	202	213			
Liver					
Lymphocytic foci, slight	209	213,215,219	228,229,230	233,236,237 238,239,240	241,242,243 244,245,250
Necrosis, slight focal	205,208	217			
Necrosis, slight focal and WBC foci, slight	207				
White blood cell foci, slight	201		225		
Lung					
Alveolar collapse; chronic respiratory disease	207,208	218,220		234,238	
Alveolar distension; chronic respiratory disease	210				
Alveolar collapse and distension; chronic respiratory disease	201,202,203 204,206,209	211,212,214 215,216,217 219	222,223,225 226,227,228 229	231,233,235 236,239,240	241,242,243 245,247,248 249,250
Alveolar collapse and distension; chronic purulent bronchietasis; chronic respiratory disease	205	213		232	

* Positive control (LAP).

Table 262

MICROSCOPIC LESIONS IN FEMALE RATS AFTER 4 WEEKS OF LAP(I) TREATMENT

(Concluded)

Organ/Lesion	Dose Level (mg/kg/day)				
	0	0.3%*	0.003%	0.03%	0.3%
	Group Designation				
	D0	D1	D2	D3	D4
	Animal Number				
Lung					
Alveolar collapse and distension;					
hemorrhage; chronic respiratory disease			221,224,230		
Alveolar collapse and distension; chronic					
purulent bronchiectasis; bronchopneumonia;					
chronic respiratory disease				237	
Alveolar collapse, hemorrhage; chronic					
purulent bronchiectasis; chronic					
respiratory disease					244
Lymph node					
Hemorrhage, slight focal					247
Spleen					
Hemosiderosis		212,213,214			
		216,217,218			
		219,220			
Thymus					
Ductal adenocarcinoma	208				
Trachea					
Tracheitis	201,202,206	211,214,217	223,227,228	231,234,235	241,242,243
	207,208,209	219		237,238,239	245,247,248
				240	
Uterus					
Dilation, moderate			223,225		242,244,249

PART 5 - OTHER PHASE II STUDIES

IN VIVO CYTOGENETICS AND *IN VITRO* DNA REPAIR TESTING

To determine whether TNT or LAP induce genetic damage to mammalian cells, we selected two studies: (a) *in vivo* cytogenetic analyses of bone marrow cells from rats, and (b) measurement of unscheduled DNA synthesis (UDS) in human diploid fibroblasts (WI-38 cells) *in vitro*.

In vivo cytogenetic analyses are used to determine whether damage to chromosomes can be induced in the whole animal. The hypothesis is that if cytogenetic aberrations are found, the compound under investigation reached the somatic cells in an activated form and induced primary DNA damage, followed by an extent of mutagenesis sufficient to alter chromosome number and/or morphology. Therefore, the induction of *in vivo* cytogenetic aberrations encompasses a complex series of events--uptake, transport, whole-animal metabolism, extensive genetic damage, cell proliferation--that cannot be evaluated in an *in vitro* test such as UDS.

In Vivo Cytogenetics Analyses - TNT and LAP

In vivo cytogenetics analyses were performed on bone marrow cells from rats that had been treated chronically (for 28 days) with two doses each of TNT and LAP and from rats that had received the chronic treatments followed by a 28-day recovery period. The selection of the two dose levels used, one high and one low, was based on the results of the subacute studies on TNT and LAP in rats. They were, respectively, 0.25 and 0.002% TNT and 0.5 and 0.005% LAP mixed in the feed. The negative control was the normal diet. High doses were the highest tolerable, so some deaths were to be expected. The positive control animals had the same diet as the negative control animals, but 24 hours before sacrifice they received a single injection of 0.375 mg/kg triethylenemelamine (TEM), which produces defects in chromosomes.[38] Young male Sprague-Dawley rats, each weighing 150 to 180 g at the initiation of treatment, were used. The low-dose, positive control, and negative control groups contained 12 rats, and the high-dose group contained 18 rats. Five animals from each treatment group were selected randomly for sacrifice 6 hours after the last administration of the compounds, and another five were killed after the 28-day recovery period.

Part 5

All laboratory practices followed for rats in the subacute studies were followed here, except that the group size and body weights permitted housing three to a cage. Also, at sacrifice, the heart, liver, kidneys, spleen, and gonads of each animal were only weighed, not preserved. These data served as reference only and are not reported.

Methods

Our procedure for in vivo cytogenetic evaluation of rat bone marrow cells was a modification of the one outlined by Nichols et al.[39] To obtain a higher population of cells in metaphase, we injected the animals with 0.75 mg/kg of colchicine 1.5 hours before sacrificing them in a CO_2 atmosphere. Bone marrow cells were aspirated from the distal end of the femur into a syringe containing Hanks balanced salt solution (HBSS). This procedure was performed on both legs of each animal, and the cell suspensions from each animal were combined in one centrifuge tube. The cells were centrifuged, and the supernatant was aspirated. The cells then were resuspended in 4.0 ml of 0.55% KCl and placed in a water bath at 37° C for 20 minutes. At this time, the cells were again centrifuged, and the supernatant was discarded. The cells were resuspended in chilled Carnoy's fixative (methanol: acetic acid, 3:1). The fixative was changed at least twice before preparation of a minimum of two slides per animal by the air-dry technique. The cells were stained with Aceto-orcein, and coverslips were attached with Permount.

Permanent slides were divided into two identical groups. The slides in each group were mixed separately at random and coded by an individual not involved in the reading and scoring. Thus, no one scoring the slides knew which slide was being read or was able to compare similar code numbers in each group. Slides were not decoded until all slides in each group had been read completely.

Slides are scored for both mitotic index and chromosomal aberrations. Mitotic indices are calculated based on 1000 cells per slide. When possible, at least 50 metaphase cells per animal are analyzed for evidence of chromosomal aberrations such as aneuploidy, polyploidy, chromosome and chromatid breaks and gaps, exchanges, dicentrics, other marker chromosomes, unusual morphology such as "stickiness" or pulverization of the chromosomes, and degree of multiple aberrations, as defined in the glossary (Exhibit A).

Exhibit A

GLOSSARY OF CYTOGENETIC ABERRATIONS

Chromatid aberration appears on only one arm of the chromosome and is a postreplicative event.

Chromosome aberrations are present in both chromatids at identical sites.

Gap is any aligned discontinuity (nonstaining region) in the chromatin that is equal to or less than the width of the chromatid or that contains visible material connecting the proximal and distal portions. Because a gap may be an artifact of slide preparation, the presence of a gap in an otherwise normal cell does not warrant considering the cell to have a cytogenetic aberration.

Break is any separation in the chromatin that exceeds the width of the chromatid or a separation accompanied by the disturbance of axial integrity.

Pulverization is extreme fragmentation of the chromatid material. It is recognized by its severity and the absence of markers.

Marker is a unique chromosomal aberration that can be easily identified and classified as follows:

- Exchange--A chromosomal translocation figure characterized by unique constellation of the chromosomal arms (triradials, quadriradials); also called somatic crossovers.
- Dicentric--A chromosome with two centromeres.
- Ring--A chromosome whose ends have joined to form a double or single circle, with or without a centromere.

More than nine aberrations per cell--each type of aberration (up to nine) is individually tabulated. Each scored type of aberration counts as one visual aberration whether it be chromatid or chromosomal; e.g., a chromatic break counts as one, a chromosomal break counts as one; dicentric, ring, or exchange figures each count as one aberration.

Polyploidy is an increase in chromosome number in excess of the diploid in an even multiple of the haploid number.

Aneuploidy is an irregular number of chromosomes, not a multiple of the haploid set, but individual chromosomes are missing or present in a multiple state (hypodiploid and hyperdiploid). The extent of aneuploidy is indicated by tabulation of the average number of chromosomes per cell.

Results

None of the rats that received the TNT high dose and none of the positive controls died prematurely. Ten of the 18 rats at the 0.5% LAP level died during the 28-day treatment period.

Table 263 presents the cytogenetic evaluation of the rats exposed to TNT, and Table 264 presents the cytogenetic evaluation of the rats exposed to LAP. No significant loss of chromosomes was observed in any of the treated animals; the average numbers of chromosomes for each treatment as well as for the negative control animals were within the same range, 39.7 to 40.8. The diploid number of chromosomes for rats is 42; the uniform reduction in average chromosome numbers from this value represents a random loss of chromosomes from the cells during the preparation of slides.

Mitotic indices were greatly depressed in the positive control rats, and we could not locate a sufficient number of dividing cells on the slides to perform cytogenetic evaluations on 50 cells for each animal. Mitotic indices were also depressed in rats exposed to the high dose of TNT, and a dose-related depression in the mitotic indices was observed in the animals exposed to LAP. However, sufficient cells were present from these animals to evaluate 50 cells per sample.

No cytogenetic abnormalities were observed other than the significant number of aberrations induced in positive control animals. Therefore, except for depressions in mitotic indices, no unusual effects were observed after chronic exposure of rats to the high and low doses of TNT and LAP.

The rats that received chronic exposures to TNT and to LAP followed by a 28-day recovery period were sacrificed and the slides were prepared before we had completed cytogenetic evaluations and decoded the slides for the animals sacrificed immediately after treatment. No high-dose LAP rats were included in the recovery groups because only 8 of the 18 rats survived this exposure. All eight were sacrificed and cytogenetic preparations were made at the end of the chronic exposure. However, the mitotic indices proved to be sufficiently high so that we evaluated randomly selected preparations from only five of the eight rats.

Further cytogenetic evaluation of samples from the recovery groups was not warranted because no cytogenetic aberrations were detected after the chronic exposures; nevertheless, we determined the mitotic indices of the recovery groups of animals for both doses of TNT and for the low dose of LAP to learn whether the mitotic indices returned to negative control values. A comparison of the values obtained on rats permitted a 28-day recovery period after the 28-day treatment with the values obtained on rats sacrificed immediately after treatment indicated that the proliferative capacity of the bone marrow cells

returned to a normal level within 28 days for the high-dose TNT group (Table 265). Following 28 days of recovery from the low dose (0.005%) of LAP, the mitotic index actually exceeded negative control values (Table 266).

Discussion and Conclusions

As described in Parts 2 and 3 of this report, we observed severe weight loss in the rats treated with TNT and LAP, particularly in those administered the high dose of LAP. This loss of weight appeared to be attributable to the reluctance of the rats to consume the food rather than to toxic effects of the compound. The absence of cytogenetic aberrations in the treated animals and the reduced proliferative capacity of the bone marrow cells, as indicated by depressions in mitotic indices, indicated that the weight loss probably was attributable more to malnutrition of the animals than to chemical cytotoxicity. This conclusion is supported by the observation that the resumption of a normal diet resulted in a recovery of the proliferative capacity of the bone marrow cells.

In other cytogenetic studies in the past, we have frequently observed mutagenic effects at near-toxic doses of the test compounds. However, no such effects were observed for TNT or LAP. Therefore, in view of the positive mutagenicity results observed in the microbial testing (described in Part 1 of this report), we hypothesize that if the compounds cannot be shown to be mutagenic *in vivo* in mammalian cells, either the rats ingested insufficient quantities of the compound to induce genetic damage to the somatic cells or the compounds were metabolically deactivated before they reached the bone marrow of the rats. However, based on the results of these cytogenetics studies, we find no evidence to support the conclusion that genetic damage can be induced by TNT or LAP *in vivo*.

Unscheduled DNA Synthesis Assays on TNT, RDX, and LAP

Unscheduled DNA synthesis (UDS) is a form of repair synthesis that involves at least two processes. First, an agent interacts with and thus damages the DNA. This is followed by incorporation of nucleotides to repair the DNA. UDS assays are based on an indirect measurement of primary DNA damage; that is, the unscheduled synthesis is indicated by the incorporation of tritiated thymidine into the DNA of the cells during repair. If the DNA damage is so excessive that it cannot be sufficiently corrected by the mechanisms of repair available to the cells, the nonrepair or incorrect repair of the DNA may be considered as a primary event leading to mutagenesis and/or to carcinogenesis.

UDS occurs in a wide variety of cell types, and it may be considered to be fairly universal because it has been observed in all stages of the cell cycle (G_0, G_1, G_2, and M) other than S, the normal synthetic phase.[40,41] (UDS is not observed during S-phase because the high level of incorporation of nucleotides during scheduled DNA synthesis obscures the relatively low level of incorporation during UDS.)

Many mutagenic and carcinogenic agents have been shown to induce UDS in an in vitro tissue culture system of cells.[42] However, other chemicals are ineffective in producing DNA damage except in a metabolically active environment. With metabolic activation, such chemicals are converted to mutagenic and/or carcinogenic intermediates that produce the damage. To incorporate a metabolic activation system into the UDS assay, a preparation containing microsomes from a mammalian liver homogenate is added to the test system. Thus, we routinely perform a parallel series of UDS assays in the presence and in the absence of a metabolically active system.

Methods

Cell culture. WI-38 cells (human fibroblasts) grown in T-25 tissue culture flasks were used for the UDS assays with TNT, RDX, and LAP. Replicate cultures of these cells were initiated in Eagle's Basal Medium containing 10% (v/v) fetal calf serum. The cells were grown to confluency and maintained in medium containing 0.5% serum for 5 to 6 days preceding the UDS assays.* This produced contact-inhibited cells in synchronous cultures in the G_0 phase of the mitotic cycle. To reduce the possibility of incorporation of tritiated thymidine (^{3}H-TdR) by an occasional S-phase cell that might have escaped the contact-inhibition synchrony and thus might obscure measurements of UDS, the cultures were preincubated for 1 hour with 10^{-2} M hydroxyurea (HU) before each assay, and 10^{-2} M HU was added during each subsequent step of the assays.

Dilution of compounds. Immediately before each assay, TNT, RDX, or LAP was diluted in dimethylsulfoxide (DMSO) to form a series of concentrations that, when diluted into culture medium, yielded the appropriate set of test concentrations. The final concentration of DMSO was maintained at 1% or less, thus minimizing the possibility of a cytotoxic effect in response to the solvent.

* As a check against the presence of mycoplasma, which could incorporate tritiated thymidine and thus obscure measurements of UDS, stock cultures were periodically cultured on Difco Beef Heart Infusion agar or broth; Microbiological Associates analyzed them for the presence of mycoplasma, and the results of these analyses were consistently negative.

Metabolic activation. For testing with metabolic activation, we used a preparation consisting of the 9000 x g supernatant of a liver homogenate (250 mg of liver/ml) from adult male Swiss-Webster mice. To this were added the following cofactors: nicotinamide, 3.05 mg/ml; glucose-6-phosphate, 16.1 mg/ml; $MgCl_2 \cdot 6H_2O$, 5.08 mg/ml; and NADP, 0.765 mg/ml.

Controls. The positive controls were 4-nitroquinoline-N-oxide (4NQO), a compound that induces UDS in the absence of metabolic activation, and dimethylnitrosamine (DMN), a compound that induces UDS in vitro only with metabolic activation. The negative control was DMSO diluted in culture medium.

Preliminary tests. Preliminary testing was performed according to the procedures described for UDS assays except that:

(1) A broader dose range was tested.

(2) Fewer replicate samples were tested at each concentration.

(3) The end-point indicator was either an apparent elevation in ^{3}H-TdR incorporation into DNA or a cytotoxic effect, as indicated by either a reduction in ^{3}H-TdR incorporation or a loss of cells from the culture, observed as a reduction in the DNA content of the culture.

The preliminary assays were performed to establish the appropriate ranges of concentrations to be tested in the actual UDS assays. These concentrations are selected according to the following criteria:

(1) If a positive response is indicated by the preliminary assay, concentrations that could confirm the response and possibly define a dose-response relationship are tested.

(2) In the absence of a preliminary indication of a positive response, concentrations are tested that are expected to cover a range between cytotoxic effects and no effects.

(3) If neither a positive response nor cytotoxic effects are indicated by the preliminary assay, the range of test concentrations includes the maximum feasible concentrations under the constraints of the solubility of the compound and the protocols as described ("Dilution of Compounds").

UDS Assays. The contact-inhibited WI-38 cells were incubated at 37° C with dilutions of TNT, RDX, or LAP and with 1 µCi/ml of ^{3}H-TdR (sp act, 6.7 Ci/mmole). For testing in the absence of metabolic activation, the cells were exposed simultaneously to TNT, RDX, or LAP and to ^{3}H-TdR for 3 hours. For testing with metabolic activation, the cells were incubated with TNT, RDX, or LAP, ^{3}H-TdR, and the metabolic

preparation for 1 hour, rinsed, and then incubated with only ^{3}H-TdR in culture medium for an additional 3 hours. (The shorter exposure time for metabolic activation testing prevents cytotoxic effects to the WI-38 cells by the liver homogenate preparation.) To extract DNA from the cells, we used a modification of the PCA-hydrolysis procedure;[43] one aliquot of the DNA solution was used to measure the DNA content, after reaction with diphenylamine,[44] and a second aliquot was used for scintillation counting measurements of the extent of incorporation of ^{3}H-TdR. Results were expressed as disintegrations per minute (dpm) of incorporated ^{3}H-TdR per unit of DNA and were compared with the rate of incorporation of ^{3}H-TdR into cells exposed to solvent only (negative control).

We have defined as an acceptable assay one in which the response of the positive control compound is predicted, within the 95% confidence limits, by least-squares regressions[42] of average dpm/μg DNA versus average dpm/μg for background. The regressions that follow are based on data that we have acquired in previous testing:

Type of Testing	Regression*	Size (n)	Correlation Coefficient (r)
Without metabolic activation	$Y_1 = 629 \pm 16.42\ (X)$†	55	0.8066
With metabolic activation	$Y_2 = 212 \pm 2.11\ (X)$†	25	0.8307

If the observed average level of incorporation for the positive control compound is outside the 95% confidence limits of the regression, we assume that some variation has occurred in the experimental procedures and the test is repeated.

<u>Interpretation of results</u>. We have tested 40 compounds that, based on the results of *in vivo* bioassays, have defined carcinogenic activity. We have analyzed the results using either the parametric One-Way Classification Analysis of Variance or the nonparametric Kruskal-Wallis One-Way Analysis of Variance, depending on which was more appropriate.‡

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* Regressions over a range of background dpm/μg DNA of 0 to 450.

† Y_1 = Average dpm/μg DNA for 10^5 M 4NQO (positive control).
Y_2 = Average dpm/μg DNA for 5×10^2 M DMN (positive control).
X = Average dpm/μg DNA for background (negative control).

‡ If there is reason to believe that the variances of each of the treatments in a test are equal (i.e., Bartlett's test of the variance is negative), the parametric analysis is the appropriate one. If the variances are not equal, the nonparametric analysis is the appropriate one.[46,47]

Of the 16 compounds generally recognized as being direct-acting carcinogens, 15 induced statistically significant elevations in the incorporation of ^{3}H-TdR into DNA at the 99% confidence level. Dose-response relationships were also observed for all but three of these. The assay of the sixteenth carcinogen, p-rosaniline, failed to suggest a positive response. The testing of the 12 compounds reported to be noncarcinogenic did not indicate any statistically significant response. Thus, the criterion of 99% confidence limits of the statistical analyses coupled with the indication of a dose-response relationship apparently can be used with reasonable accuracy to predict the biological significance of the UDS response to an ultimate carcinogen or noncarcinogen.

The correlation between a UDS response and biological significance for testing with metabolic activation is less clear. Of the 12 procarcinogens (compounds requiring chemical modifications to become active) that we have tested with metabolic activation, seven induced statistically significant increases in ^{3}H-TdR uptake at the 99% confidence level; in addition, the results of all seven of these tests indicated a dose-response relationship. The remaining five procarcinogens failed to induce any increase in ^{3}H-TdR incorporation. Thus, the metabolic activation preparation now used for UDS testing apparently is capable of activating only a portion of the spectrum of the procarcinogens, and the lack of a response in testing with metabolic activation cannot be assumed to be indicative of an absence of potential biological hazard.

Results and Discussion

Table 267 presents the results of the preliminary assay of TNT without metabolic activation. The levels of ^{3}H-TdR incorporation in response to treatments with the lower concentrations of TNT were equivalent to that of the control. The response to the highest concentration could not, however, be accurately estimated due to the discoloration of these samples (hydrolyzed DNA solutions from these samples were yellow rather than clear, thus affecting the colorimetric determination of DNA content). Therefore, the testing of TNT was limited to concentrations that would not discolor the samples. Based on these observations, we selected 1000 µg/ml as the highest test concentration of TNT for assay in the absence of metabolic activation. The results of this assay (Table 268) indicated a statistically significant elevation in H-TdR incorporation ($F_{3,20} = 38.58 > 4.94$)*

* F is the statistic generated by the parametric analysis of variance, and is compared to the value of F at which there is a 1% probability that the observed variations in the data could be due to random selection.

at the 99% confidence level. However, the discoloration of the samples tested with the two highest concentrations of TNT made it impossible to clearly distinguish a dose-response relationship for the apparent increase in ^{3}H-TdR incorporation. Since only one of the criteria for a positive response was clearly met, we can conclude only that UDS was suggested in this test.

The results of the preliminary assay of TNT in the presence of metabolic activation (Table 269) suggested neither a positive response nor a cytotoxic effect. (Discoloration of the test samples was not observed in this assay.) Therefore, the solubility of TNT limited the maximum test concentration for the UDS assay of TNT with metabolic activation. Table 270 presents the results of this assay. UDS was not observed in this test, as the levels of ^{3}H-TdR incorporation were statistically indistinguishable from the control at 99% confidence ($F_{5,30}$ = 2.76 < 3.70).

An elevation in H-TdR incorporation in response to treatment with RDX at 2000 μg/ml was suggested by the results of the preliminary assay of this compound (Table 271). Therefore, test concentrations that could further define the suggested response were selected for the UDS assay of RDX without metabolic activation. The results of this assay (Table 272) did not confirm the response suggested by the preliminary assay, because none of the levels of ^{3}H-TdR incorporation were statistically greater than the control. Thus, UDS was not observed in response to treatment with RDX in the absence of metabolic activation.

The results of the preliminary assay of RDX with metabolic activation (Table 273) indicated no observable effects on cells exposed to concentrations as high as 4000 μg/ml, since all ^{3}H-TdR incorporation levels were consistent with the control. The concentration of 4000 μg/ml RDX was also observed to be the maximum feasible test concentration based on the solubility of RDX. Therefore, the UDS assay of RDX with metabolic activation was limited to a maximum test concentration of 4000 μg/ml, which was expected to be below a threshold for cytotoxic effects. Table 274 presents the results of this assay. As anticipated, cytotoxic effects were not observed. Furthermore, all levels of ^{3}H-TdR were statistically indistinguishable from the control ($F_{5,30}$ = 1.48 < 3.70). Therefore, we can conclude only that UDS was not observed in response to RDX with metabolic activation, within the concentration range tested.

Tables 275 and 276 present the results of the preliminary assays of LAP without and with metabolic activation, respectively. In each case, neither cytotoxic effects nor a positive response was indicated by these results. Therefore, in the UDS assays of LAP in the absence and presence of metabolic activation, the solubility of this material limited the testing to a maximum concentration of 8000 μg/ml. The results of the UDS assay of LAP without metabolic activation (Table 277) were similar to those of the preliminary assay in that all treatment

effects were statistically equal ($F_{5,29} = 2.21 < 3.73$). Thus, under this test condition, neither UDS nor cytotoxic effects were observed. The results of the UDS assay of LAP with metabolic activation (Table 278) appeared to indicate a positive response. The One-Way Classification Analysis of Variance of these data indicated that at the 99% confidence level, the treatment effects are not equal ($F_{5,30} = 4.40 > 3.70$). Furthermore, it can be demonstrated that the response to treatment with 8000 µg/ml LAP is statistically greater than the response to the control treatment at this level of significance. However, a dose-response relationship for the response, although suggested, is not clearly demonstrated by these results. We believe that it would be necessary to test LAP at concentrations in excess of 8000 µg/ml with metabolic activation to clearly demonstrate a dose-response relationship. Since such an assay is incompatible with our test procedures, we are unable to accurately assess the biological significance of the observed response. Thus, we can conclude only that the results of the testing of LAP with metabolic activation suggest a UDS response.

In summary, based on our criteria for a biologically significant response, UDS was suggested as a consequence of treatment of human cells with TNT in the absence of metabolic activation and with LAP in the presence of metabolic activation. However, UDS was not observed in response to treatment with LAP in the absence of metabolic activation, with TNT in the presence of metabolic activation, or with RDX either with or without metabolic activation.

ENZYME INDUCTION STUDIES

Dogs, rats, and mice that were dosed with TNT or LAP either died when administered high doses or, if they survived 2 weeks of treatment, tolerated the compounds and recovered partially from the toxic symptoms of loss of appetite and weight. A possible explanation for the partial recovery observed is that repeated administration of the compounds resulted in an accelerated rate of detoxification.

The experiments described here were conducted to test the hypothesis that TNT, RDX, or LAP might stimulate the hepatic microsomal enzyme systems.

Methods

Adult Sprague-Dawley rats of both sexes were fed diets containing 0.1% RDX, 0.25% TNT, or 0.25% LAP (TNT/RDX, 1.6/1) for 3 weeks. Control rats and positive control rats were fed the normal diet. The positive control rats were treated with phenobarbital during the last 5 days of the 3-week experimental period. Phenobarbital was injected

ip (40 mg/kg, twice daily) on Days 1, 4, and 5. On Days 2 and 3 (weekend), the rats were given phenobarbital in their drinking water (0.57 g/l). After 3 weeks of dietary treatment or 5 days of phenobarbital treatment (positive controls), the rats were killed by decapitation, and their livers were removed.

Rat liver was homogenized in three volumes of 1.15% KCl in 0.01 M phosphate, pH 7.4. After centrifugation at 10,000 x *g* for 10 minutes, the supernatant fraction was carefully removed and used for incubation. Each beaker contained 1 ml of the supernatant; 1 ml of 0.1 M phosphate, pH 7.4; 0.5 ml of cofactors (1 μmole NADP, 25 μmoles $MgCl_2$, 15 μmoles nicotinamide, and 25 μmoles glucose-6-phosphate); and 0.5 ml of substrates (10 μmoles of aniline or aminopyrine or 7 μmoles of o-nitroanisole). Incubation was at 37° for 30 minutes. The products o-aminophenol, 4-aminoantipyrine, and o-nitrophenol were assayed colorimetrically.

For investigation of whether various pretreatments produced alterations in the metabolic pattern of TNT, two male and two female rats from each group were orally administered 9 μCi of ^{14}C-ring-labeled TNT 1 day before sacrifice, and 24-hour urine specimens were collected. Aliquots of the urine samples were subjected to benzene extraction, followed by an extraction with ethyl acetate at pH 1. The organic fractions were assayed for radioactivity in a Searle Analytic Mark III liquid scintillation counter.

Results

Substrates used for testing enzyme induction represented three metabolic pathways: N-demethylation of aminopyrine, O-demethylation of o-nitroanisole, and aromatic ring hydroxylation of aniline. These generally respond to all types of inducers, including drugs and pesticides. All these reactions are oxidative, whereas the primary metabolic transformation of TNT is nitro-group reduction and, to a lesser extent, oxidation of the methyl group.

As Table 279 shows, phenobarbital stimulated the metabolism of all three test substances by the liver in both sexes. TNT, RDX, and LAP showed no stimulatory activities in the metabolism of aminopyrine (N-demethylation) or aniline (aromatic hydroxylation). However, these compounds apparently can act as microsomal enzyme inducers to a limited extent, as evidenced by stimulation of the metabolism of o-nitroanisole (O-demethylation).

As shown in Table 280, after a single oral dose of ^{14}C-ring-labeled TNT, approximately 50% and 20% of the administered dose were found in the urine and feces, respectively, after 24 hours. When urine samples were extracted with benzene, approximately 20% of the radioactivity present in the samples was extracted. A control extraction experiment

with standard ^{14}C-labeled TNT showed that benzene extracted 96 to 98% of TNT. Since the percentages of the radioactivity extracted by benzene were essentially identical in all experimental groups, the percentage of unchanged TNT being excreted apparently was not altered by pretreatment of the rats with phenobarbital, RDX, or TNT.

The residual counts after benzene extraction were extracted with ethyl acetate. Approximately 50% of the radioactivity present in the urine samples appeared in ethyl acetate. These are considered to be unconjugated metabolites of TNT. Thin-layer chromatography of the extract revealed as many as three metabolites.

Data presented in Table 280 indicate that LAP pretreatment may have increased the percentage of ethyl acetate-extractable metabolites in both sexes and that TNT pretreatment may have increased the ethyl acetate-extractable metabolites in the female. Since the data are based on only two rats from each treatment group, a definite conclusion cannot be drawn.

Discussion and Conclusions

Lemburg and Callaghan[48,49] reported that rats orally given TNT (5 to 40 mg) excreted 15 to 20% of TNT in urine unchanged; our data (benzene fraction) are in agreement. They further observed that repeated dosing did not alter the excretion pattern, suggesting that there was no storage of TNT or metabolites.

TNT is metabolized by nitro-group reduction, ring hydroxylation, and oxidation of the methyl group. All these reactions are known to be catalyzed by the hepatic microsomal mixed-function oxidases. RDX is extensively metabolized to CO_2 and the intracellular site of the metabolism of this compound has not been reported.

Since many compounds that are metabolized by the hepatic microsomes stimulate (induce) the microsomal enzymes, it was of interest to investigate whether TNT has the microsomal enzyme-inducing property. The present data indicate that TNT and RDX show limited capacities for enzyme induction. Only one of the three metabolic pathways measured was stimulated by these compounds.

The metabolism of TNT based on measurement of benzene-extractable radioactivity, however, was not altered by pretreatment of the rat with phenobarbital, TNT, or RDX. Thus, decreased toxicologic manifestation to repeated dosing of TNT apparently cannot be explained on the basis of increased metabolic disposition of TNT. However, we cannot rule out the possibility that the composition of the metabolites of TNT may have been altered by repeated dosing of TNT. Further studies are required to clarify this point.

Table 263

CYTOGENETIC EVALUATION OF BONE MARROW CELLS FROM RATS TREATED WITH TNT FOR 28 DAYS

	Negative Control	Dosage of TNT Low (0.002%)	Dosage of TNT High (0.25%)	Positive Control*
Total number of cells scored	250	250	250	233
Average number of chromosomes/cell	40.27	40.56	40.74	40.14
Mitotic index† (percent)	1.4%	1.3%	1.0%	0.6%
Cells with aberrations				
Breaks with fragments	0	0	0	0.4
Chromosome	0	0	0	0.4
Chromatid	0	0	0	11.2
Breaks without fragments				
Chromosome	0	0	0	0
Chromatid	0	0	0	3.4
Marker chromosomes				
Exchanges	0	0	0	23.2
Dicentrics	0	0	0	1.3
Rings	0	0	0	0.4
More than one type of aberration/cell	0	0	0	11.2
More than nine aberrations/cell	0	0	0	11.2
Total cells with aberrations	0	0	0	40.3
Normal cells				
Normal cells with gaps	0	0	0.4	0.4
Normal cells without gaps	100.0	100.0	99.6	59.3
Total normal cells	100.0	100.0	100.0	59.7

*In vivo treatment with TEM (0.375 mg/kg) for 24 hours.

†Mitotic indices based on 1000 cells per sample.

Table 264

CYTOGENETIC EVALUATION OF BONE MARROW CELLS FROM RATS TREATED WITH LAP FOR 28 DAYS

	Negative Control	Dosage of LAP		Positive Control*
		Low (0.005%)	High (0.5%)	
Total number of cells scored	250	250	250	127
Average number of chromosomes/cell	40.20	40.74	39.73	40.58
Mitotic index† (percent)	1.3%	1.0%	0.5%	0.4%
Cells with aberrations (percent)				
Breaks with fragments				
Chromosome	0	0	0	0
Chromatid	0	0	0	15.0
Breaks without fragments				
Chromosome	0	0	0	0
Chromatid	0	0	0	0.8
Marker chromosomes				
Exchanges	0	0	0	16.5
Dicentrics	0	0	0	2.4
Rings	0	0	0	0.8
More than one type of aberration/cell	0	0	0	9.4
More than nine aberrations/cell	0	0	0	10.2
Total cells with aberrations	0	0	0	30.7
Normal Cells				
Normal cells with gaps	0	0.4	0	0
Normal cells without gaps	100.0	99.6	100.0	69.3
Total normal cells	100.0	100.0	100.0	69.3

*In vivo treatment with TEM (0.375 mg/kg) for 24 hr.

†Mitotic indices based on 1000 cells per sample.

Table 265

MITOTIC INDICES OF BONE MARROW CELLS FROM RATS
AFTER 4 WEEKS OF TNT TREATMENT
WITH OR WITHOUT 4 WEEKS OF RECOVERY

	Negative Control	Dose of TNT Low (0.002%)	High (0.25%)	Positive Control
After treatment only	1.4%	1.3%	1.0%	0.6%
After treatment and recovery	1.6%	1.7%	1.4%	0.8%

Reported mitotic indices are the mean of results from 5 rats for which 1000 cells were counted per rat.

Table 266

MITOTIC INDICES OF BONE MARROW CELLS FROM RATS
AFTER 4 WEEKS OF LAP TREATMENT
WITH OR WITHOUT 4 WEEKS OF RECOVERY

	Negative Control	Low (0.005%)	High (0.5%)	Positive Control
After treatment only	1.3%	1.0%	0.5%	0.4%
After treatment and recovery	1.6%	2.5%	--	0.8%

Reported mitotic indices are the mean of results from 5 rats for which 1000 cells were counted per rat.

Table 267

PRELIMINARY UNSCHEDULED DNA SYNTHESIS ASSAY OF TNT
(dpm/μg DNA)

	Concentration of Compounds Tested					
	TNT (μg/ml)					4NQO (M)
Sample	0*	2	20	200†	2000†	10^{-5}
1	60	36	28	38	--‡	1398
2	51	44	38	38	--‡	1469
3	39	44	41	40	--‡	1279
4	47	44	66	38	--‡	1588
Mean	49	42	44	38		1434
SD	9	4	16	1		129
SE	4	2	8	1		65

*Negative control and compound solvent, 1.0% DMSO.

†Precipitates observed at 200 μg/ml and 2000 μg/ml.

‡Quantity of DNA impossible to determine due to discoloration of samples.

Table 268

UNSCHEDULED DNA SYNTHESIS ASSAY OF TNT
(dpm/μg DNA)

	Concentration of Compounds Tested						
	TNT (μg/ml)						4NQO (M)
Sample	0*	62.5	125	250†	500†	1000†	10^{-5}
1	64	38	49	75	74††	84††	1201
2	49	40	50	77	64††	65††	1428
3	38	39	38	73	65††	74††	1174
4	37	36	40	79	79††	63††	1037
5	37	37	36	67	59††	61††	1140
6	48	34	37	85	78††	81††	1144
Mean	45	40	42	76	70††	71††	1187
SD	10	5	6	6	8††	10††	130
SE	4	2	2	2	3††	4††	53

*Negative control and compound solvent, 0.5% DMSO.

†Precipitates observed at 250, 500, and 1000 μg/ml.

††These values may be inaccurate due to slight yellow discoloration of the samples.

Table 269

PRELIMINARY UNSCHEDULED DNA SYNTHESIS ASSAY OF TNT
WITH METABOLIC ACTIVATION
(dpm/μg DNA)

	Concentration of Compounds Tested					
	TNT (μg/ml)					DMN (M)
Sample	0*	6	60	600†	6000†	5×10^{-2}
1	45	41	46	48	57	283
2	46	54	54	47	58	305
3	42	36	44	53	53	286
4	48	56	47	62	49	323
Mean	45	47	48	52	54	299
SD	3	10	5	7	4	19
SE	1	5	2	3	2	9

*Negative control and compound solvent, 1.0% DMSO.
†Precipitates observed at 600 and 6000 μg/ml.

Table 270

UNSCHEDULED DNA SYNTHESIS ASSAY OF TNT WITH METABOLIC ACTIVATION
(dpm/µg DNA)

Sample	Concentration of Compounds Tested: TNT (µg/ml) 0*	375†	750†	1500†	3000†	6000†	DMN (M) 5 x 10^{-2}
1	63	46	60	62	61	68	282
2	62	53	66	55	54	87	296
3	72	65	96	65	54	95	360
4	58	51	93	63	51	65	308
5	60	68	63	53	58	58	510
6	66	41	54	76	72	71	379
Mean	64	54	72	62	59	74	356
SD	5	1[illegible]	18	8	8	14	84
SE	2	4	7	3	3	6	34

*Negative control and compound solvent, 0.5% DMSO.

†Precipitates observed at all concentrations.

Table 271

PRELIMINARY UNSCHEDULED DNA SYNTHESIS ASSAY OF RDX
(dpm/μg DNA)

	Concentration of Compounds Tested					
	RDX (μg/ml)					4NQO (M)
Sample	0*	2	20	200†	2000†	10^{-5}
1	36	37	26	30	53	1081
2	32	35	46	27	50	1057
3	40	31	62	36	53	1040
4	34	38	24	43	53	1107
Mean	36	35	39	34	52	1071
SD	3	3	18	7	2	29
SE	2	1	9	4	1	14

*Negative control and compound solvent, 1.0% DMSO.

†Precipitates observed at 200 μg/ml and 2000 μg/ml.

Table 272

UNSCHEDULED DNA SYNTHESIS ASSAY OF RDX
(dpm/μg DNA)

	Concentration of Compounds Tested						
	RDX (μg/ml)						4NQO (M)
Sample	0*	250†	500†	1000†	2000†	4000†	10^{-5}
1	59	38	50	69	63	74	1558
2	45	38	70	80	48	54	1490
3	87	37	44	80	62	66	1481
4	87	33	59	70	50	76	1638
5	65	44	42	--‡	44	87	1712
6	74	38	52	65	50	70	1449
Mean	70	38	53	73	53	71	1555
SD	17	3	10	7	8	11	103
SE	7	1	4	3	3	4	42

*Negative control and compound solvent, 1.0% DMSO.

†Precipitates observed at all concentrations.

‡Sample lost.

Table 273

PRELIMINARY UNSCHEDULED DNA SYNTHESIS ASSAY OF RDX
WITH METABOLIC ACTIVATION
(dpm/μg DNA)

	Concentration of Compounds Tested					
	RDX (μg/ml)					DMN (M)
Sample	0*	4	40†	400†	4000†	5×10^{-2}
1	53	51	45	53	48	293
2	72	39	66	60	90	296
3	57	58	84	50	52	400
4	62	68	56	56	80	340
Mean	61	54	63	55	67	322
SD	8	12	16	4	21	50
SE	4	6	8	2	10	25

*Negative control and compound solvent, 1.0% DMSO.

†Precipitates observed at 40 μg/ml, 400 μg/ml and 4000 μg/ml.

Table 274

UNSCHEDULED DNA SYNTHESIS ASSAY OF RDX WITH METABOLIC ACTIVATION
(dpm/μg DNA)

	Concentration of Compounds Tested						
	RDX (μg/ml)						DMN (M)
Sample	0*	250†	500†	1000†	2000†	4000†	5×10^{-2}
1	45	41	44	51	52	44	261
2	37	43	45	43	56	54	283
3	54	44	49	37	40	50	305
4	46	42	51	47	50	45	286
5	42	34	59	47	44	56	342
6	48	47	43	57	56	44	323
Mean	45	42	48	47	50	49	300
SD	5	4	6	7	6	5	29
SE	2	2	2	3	3	2	12

*Negative control and compound solvent, 1.0% DMSO.

†Precipitates observed at all concentrations.

Table 275

PRELIMINARY UNSCHEDULED DNA SYNTHESIS ASSAY OF LAP
(dpm/μg DNA)

	Concentration of Compounds Tested					
	LAP (μg/ml)					4NQO (M)
Sample	0	4	40	400	4000*	10^{-5}
1	58	50	67	32	76	1376
2	55	59	57	40	55	1357
3	61	51	56	32	59	1412
4	68	62	58	32	60	1477
Mean	61	55	60	34	62	1406
SD	6	6	5	4	9	53
SE	3	3	3	2	4	26

*Precipitate observed at 4000 μg/ml.

Table 276

PRELIMINARY UNSCHEDULED DNA SYNTHESIS ASSAY OF LAP WITH METABOLIC ACTIVATION (dpm/μg DNA)

	Concentration of Compounds Tested					
	LAP (μg/ml)					DMN (M)
Sample	0*	4	40	400	4000†	5×10^{-2}
1	79	74	72	77	75	364
2	84	85	85	79	90	374
3	98	82	78	73	72	375
4	75	110	74	97	71	381
Mean	84	88	77	81	77	374
SD	10	15	6	11	9	7
SE	5	8	3	5	5	4

*Negative control and compound solvent, 1.0% DMSO.

†Precipitate observed at 4000 μg/ml.

Table 277

UNSCHEDULED DNA SYNTHESIS ASSAY OF LAP
(dpm/μg DNA)

	Concentration of Compounds Tested						
	LAP (μg/ml)						4NQO (M)
Sample	0*	3277†	4096†	5120†	6400†	8000†	10^{-5}
1	44	--‡	62	54	57	82	1536
2	62	59	66	52	57	95	1570
3	50	76	47	61	57	42	1684
4	48	78	53	60	60	91	1444
5	68	69	53	57	54	63	1601
6	72	48	57	61	73	72	1806
Mean	57	66	56	58	60	74	1607
SD	12	13	7	4	7	20	125
SE	5	6	3	1	3	8	51

*Negative control and compound solvent, 1.0% DMSO.

†Precipitates observed at all concentrations.

‡Sample lost.

Table 278

UNSCHEDULED DNA SYNTHESIS ASSAY OF LAP WITH METABOLIC ACTIVATION (dpm/µg DNA)

	Concentration of Compounds Tested						
	LAP (µg/ml)						DMN (M)
Sample	0*	3277†	4096†	5120†	6400†	8000†	5×10^{-2}
1	56	65	75	78	79	124	327
2	44	94	73	76	108	89	360
3	60	78	97	56	68	105	342
4	67	71	80	84	68	109	324
5	84	46	70	80	98	74	345
6	61	47	77	79	118	85	332
Mean	62	67	79	75	90	98	338
SD	13	18	10	10	21	18	13
SE	5	8	4	4	9	7	5

*Negative control and compound solvent, 1.0% DMSO.

†Precipitates observed at all concentrations.

Table 279

RAT LIVER MICROSOMAL ENZYME ASSAYS AFTER VARIOUS TREATMENTS

Group	N-Demethylation		O-Demethylation		Aromatic Hydroxylation	
	Male	Female	Male	Female	Male	Female
Control	2.88 ± 0.88*	1.13 ± 0.25	5.58 ± 1.56*	3.50 ± 1.28	8.64 ± 1.39	7.18 ± 1.27
Phenobarbital	14.61 ± 1.93[1]	3.54 ± 0.95[1]*	28.57 ± 2.42[1]	13.99 ± 2.75[1]*	25.37 ± 5.01[1]	13.36 ± 2.37[1]*
RDX 0.1%	3.62 ± 1.01	0.84 ± 0.31	11.50 ± 1.82[1]	9.64 ± 2.42[1]	10.70 ± 1.84	7.68 ± 1.78
LAP 0.25%	2.25 ± 0.53	0.86 ± 0.22	11.25 ± 2.81[2]	10.01 ± 1.88[1]	10.98 ± 3.13	7.15 ± 1.36
TNT 0.25%	1.39 ± 0.53	1.03 ± 0.40	11.09 ± 1.37[1]	11.35 ± 1.30[1]	5.34 ± 1.80	6.00 ± 0.95

Data are expressed as μmoles product formed per gram of protein in 30 minutes ± SD. Six rats constituted each group, except for those groups marked with an asterisk, which contained five rats.

Statistical significance: [1]$p < .001$
[2]$p < .005$

Table 280

URINE DATA AFTER ORAL ADMINISTRATION OF ^{14}C-RING-LABELED TNT TO RATS

Group	Percent of Administered Dose Excreted in Urine		Percent of Radioactivity* Extracted into Benzene		Percent of Radioactivity* Extracted into Ethyl Acetate	
	Male	Female	Male	Female	Male	Female
Control	48.3, 48.7	62.4, 56.4	23.6, 24.3	16.1, 17.3	40.7, 49.4	33.8, 40.6
Phenobarbital	53.3, 53.3	59.7, 59.4	21.1, 20.4	21.4, 20.4	46.0, 35.1	53.5, 43.6
LAP	49.1, 55.3	59.9, 56.3	28.0, 21.3	19.7, 20.8	59.4, 58.1	55.8, 55.7
TNT	51.3, 83.1	56.0, 65.7	24.0, 22.4	15.7, 15.7	46.3, 46.9	47.8, 49.7

* Based on total radioactivity in the urine being 100.

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Appendix A

ANALYTICAL METHODS

Appendix A

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METHOD OF CALCULATING ACUTE ORAL LD50s

Introduction

A computer program has been designed to determine the mid-lethal or mid-effective dose (LD50 or ED50) from a series of doses and quantal responses using the maximum likelihood method as described by Finney.* It calculates the response as a function (linear, natural log, or some specified power) of the dose, estimates the best straight line through these points, and then adjusts this straight line in an iterative process until the likelihood that this line is the correct regression line is at a maximum. Once this is done, the LD50 or ED50 and its percent and standard errors are calculated; the slope of the regression line and its percent and standard errors are calculated; the chi-square statistic, the degrees of freedom, and the probability that the data points fit the regression line poorly are determined; and finally, Finney's G factor and the upper and lower 95% confidence limits for the LD50 or ED50 are found.

Methods and Formulas Used

The maximum likelihood method of Finney,* which may be used for quantal dose-response relationships, involves an iterative process for solving the equation $\frac{\partial L}{\partial \phi} = 0$, where $L = \Sigma\ r_i \log P_i + \Sigma\ (n_i - r_i) \log (1 - P_i)$, n_i = sample at a particular dose, r_i = number that respond to that dose, P_i = probability that r_i respond at that dose, and ϕ = any argument of P such that P is differentiable everywhere. This method is general whatever the form of the probability distribution P,

* D. J. Finney. Probit Analysis. Cambridge University Press, England, 1971.

but, in particular, we are interested in the form

$$P = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{x} e^{\left(\frac{-(x-\mu)^2}{2\sigma^2}\right)} dx ,$$

where x is a linear, logarithmic, or other suitable function of the dose. We can measure this probability on a transformed scale (the Normal Equivalent Deviate or Y scale) by defining

$$P = \frac{1}{2\sqrt{\pi}} \int_{-\infty}^{Y} e^{\left(\frac{-u^2}{2}\right)} du$$

This is equivalent to a linear dependence of Y on x: $Y = \alpha + \beta x$, where $\mu = \frac{-\alpha}{\beta}$ and $\sigma = \frac{1}{\beta}$. Now define

$$Z = \frac{\partial P}{\partial Y} = \frac{1}{2\sqrt{\pi}} e^{\left(\frac{-Y^2}{2}\right)} .$$

Then define

$$\frac{\partial P}{\partial \alpha} = Z \text{ and } \frac{\partial P}{\partial \beta} = Zx.$$

If we guess a solution of $\frac{\partial L}{\partial \phi} = 0$ in terms of the parameters $Y_1 = a_1 + b_1 x$ (using the formula giving the <u>line of best fit</u> through a set of n points $(x_1,Y_1), (x_2,y_2),\ldots, (x_n,y_n)$: $y = mx + (\bar{y} - m\bar{x})$,

$$\bar{x} = \frac{\Sigma x_i}{n} ; \bar{y} = \frac{\Sigma y_i}{n} ; m = \left(\frac{\Sigma x_i y_i - n\bar{x}\bar{y}}{\Sigma x_i^2 - n\bar{x}^2}\right)^2,^*$$

then introduce a <u>weighting coefficient</u> $w = \frac{Z^2}{P(1-P)}$ and a <u>working probit</u> $y = Y_1 + \frac{p-P}{Z}$ (p being the empirical probability, i.e. $p = \frac{r_i}{n_i}$), we can

*S. M. Selby. Standard Mathematical Tables. The Chemical Rubber Co., Cleveland, Ohio, 1967.

solve for the correction factors δa and δb using

$(a_1 + \delta a)\Sigma n_i w_i + (b_1 + \delta b)\Sigma n_i w_i x_i = \Sigma n_i w_i y_i$ and $(a_1 + \delta a)\Sigma n_i w_i x_i + (b_1 + \delta b)\Sigma n_i w_i x_i^2$ $= \Sigma n_i w_i x_i y_i$. By letting $\bar{x} = \dfrac{\Sigma n_i w_i x_i}{\Sigma n_i w_i}$ and $\bar{y} = \dfrac{\Sigma n_i w_i y_i}{\Sigma n_i w_i}$,

we can calculate

$$b_2 = b_1 + \delta b = \frac{\Sigma n_i w_i (x_i - \bar{x})(y_i - \bar{y})}{\Sigma n_i w_i (x_i - \bar{x})^2}$$

and $a_2 = a_1 + \delta a = \bar{y} - b_2\bar{x}$. We can iterate this procedure for any desired accuracy; we choose to iterate until $\delta b < .001(b_1)$.

Then we determine:

the LD_{50}: the dose such that $0 = Y = \alpha + \beta x$, i.e. $LD_{50} = \frac{-\alpha}{\beta}$;

the Standard Error of the LD_{50}: $SE(LD_{50}) = \sqrt{\frac{1}{b^2}\left(\frac{1}{\Sigma n_i w_i} + \frac{(LD_{50} - \bar{x})^2}{\Sigma n_i w_i (x_i - \bar{x})^2}\right)}$;

the slope of the regression line: slope $= \beta$;

the Standard Error of this slope: $SE(\text{slope}) = \dfrac{1}{\Sigma n_i w_i (x_i - \bar{x})^2}$;

the number of degrees of freedom: k = number of doses − 2;

the Chi-Square statistic: $x^2 = \Sigma n_i w_i (y_i - Y_i)^2$;

The probability of poor fit: found by integrating

$F(x^2) = \int_0^{x^2} \dfrac{1}{2^{\frac{k}{2}}\,\Gamma(\frac{k}{2})}\, x^{(\frac{n-2}{2})}\, e^{(\frac{-x}{2})}\, dx$ according to Simpson's rule;

Finney's "G" factor: $$G = \frac{t_{(.95)}}{\beta^2(\Sigma n_i w_i x_i^2 - (\Sigma n_i w_i)\bar{x}^2)};$$

and the upper and lower 95% confidence limits:

$$C.\ L. = LD_{50} + \frac{G}{1-G}(LD_{50} - \bar{x}) \pm \frac{t_{(.95)}}{\beta(1-G)} \sqrt{\frac{1-G}{\Sigma n_i w_i} + \frac{(LD_{50}-\bar{x})^2}{\Sigma n_i w_i x_i^2 - (\Sigma n_i w_i)\bar{x}^2}}.$$

EYE IRRITATION TEST: SCALE FOR SCORING OCULAR LESIONS*

(1) Cornea

(A) Opacity-degree of density (area most dense taken for reading)

No opacity	0
Scattered or diffuse area, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris invisible	4

(B) Area of cornea involved

One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

A X B X 5 Total maximum = 80

(2) Iris

(A) Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, hemorrhage, gross destruction (any or all of these)	2

A X 5 Total maximum = 10

(3) Conjunctivae

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

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* Source: Food and Drug Administration. Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics. Division of Pharmacology, Food and Drug Administration, U.S. Dept. of Health, Education, and Welfare, Washington, D.C., 1959, p. 51.

(B) Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids about half closed to completely closed	4

(C) Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs, and considerable area around the eye	3

Score (A + B + C) X 2   Total maximum = 20

SKIN IRRITATION TEST: EVALUATION OF SKIN REACTIONS*

(1) Erythema and Eschar Formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Total possible erythema score	4

(2) Edema Formation

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Total possible edema score	4

* Source: Food and Drug Administration. Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics. Division of Pharmacology, Food and Drug Administration, U.S. Dept. of Health, Education, and Welfare, Washington, D.C., 1959, p. 48.

MAXIMIZATION GRADING FOR CONTACT ALLERGENICITY*

Sensitization Rate (%)	Grade	Classification
0-8	I	Weak
9-28	II	Mild
29-64	III	Moderate
65-80	IV	Strong
81-100	V	Extreme

* Source: J. B. Magnusson and A. M. Kligman. The identification of contact allergens by animal assay. The guinea pig maximization test. J. Invest. Dermatol. 52, pp. 268-276 (1969).

HEMATOLOGY AND CLINICAL CHEMISTRY METHODS

Hematology Methods - Peninsula Medical Laboratory

The methods used by Peninsula Medical Laboratory for hematological determinations are as follows.

Erythrocyte and Leukocyte Counts (RBC, WBC)

A Coulter Electronic Particle Counter with 100-μ aperture was used.[1] The instrument was standardized daily in a three-step process, as follows. The electronics was first checked in a standard procedure for proper functioning. Then the instrument was standardized for erythrocyte and leukocyte counts (as well as hemoglobin and hematocrit) against a 4C control standard (Coulter Electronics, Inc.). Finally, two blood samples that had been kept from the previous day and refrigerated were rerun for erythrocyte and leukocyte counts. Each test blood sample was counted in duplicate.

Hemoglobin (Hgb)

Hemoglobin was determined in the Coulter counter as cyanomethemoglobin.[2] Cyanomethemoglobin standards were supplied by Coulter Electronics, Inc., as part of the 4C control standard. Each test blood sample was measured in duplicate.

Hematocrit (Hct)

Hematocrit was calculated by the following equation:

$$\text{Hct} = \text{RBC}\ (10^6/\text{mm}^3) \times \text{MCV}\ (\mu^3).$$

Mean Corpuscular Volume (MCV)

MCV was determined in the Coulter Counter after (daily) standardization by the Wintrobe microhematocrit method. MCV on each test sample was determined in duplicate, and Hct was calculated from the average according to the above formula.

Mean Corpuscular Hemoglobin (MCH)

MCH was calculated as follows:

$$\text{MCH}\ (\quad \text{g}) = \frac{\text{Hgb (g \%)} \times 10}{\text{RBC}\ (10^6/\text{mm}^3)}.$$

Appendix A

Mean Corpuscular Hemoglobin Concentration (MCHC)

MCHC was calculated as follows:

$$MCHC\% \ (g \ \%) = \frac{Hgb \ (g \ \%) \times 100}{Hct}$$

Differential Leukocyte Counts

Leukocytes were stained with Wright's stain for examination and counting under the microscope. Cell types identified and counted were polymorphonuclear cells, band cells, lymphocytes, atypical lymphocytes, monocytes, eosinophils, and/or basophils.

Reticulocyte Count (Retic)

Reticulocytes were manually counted after Methylene Blue N staining, using a differential smeared slide under a microscope.

Heinz Bodies

Heinz bodies were stained with methyl-violet and the percentage was calculated. Heinz bodies were not reported in the text unless positive.

Clinical Chemistry Methods - Peninsula Medical Laboratory

The following clinical chemistry tests were performed at Peninsula Medical Laboratory on the blood samples from dogs and rats. These tests represent a SMAC-20 profile as described in the Technicon manual (Technical Publication No. UA3-0306B3, March 1976) and were done using the Technicon SMAC high-speed, computer-controlled biochemical analyzer (Technicon Instruments Corp., Tarrytown, New York). Standardization for each test was made on every forty-eighth tube (sixth rack), using the Technicon SMAC References I and II (FDA-approved) and the procedures outlined in the bulletins accompanying these references (Nos. 4060-A-R8-6/R11-7-2 and 4060 B-R4-7/R11-7-2, Technicon Instruments Corp.).

Glucose (mg %)

Blood glucose levels were determined on sera from fasted animals by a modification of the procedures of Gochman and Schmitz.[3] The method basically involves oxidation of glucose with glucose oxidase to produce H_2O_2, which then reacts with 3-methyl-2-benzothiazolinone hydrazone and dimethylasicline indicators to produce an intensely colored indamine dye for determination in the colorimeter at 37°.

Creatinine (mg %)

Creatinine is analyzed for by an automated adaptation[5] of the original method of Jaffe[6] in which the creatinine is allowed to react with saturated picric acid in alkaline solution at 37°. Analysis in the colorimeter is performed at 505 nm.

Uric Acid (mg %)

Uric acid is determined by the method of Sobrinho-Simões[7] as modified by Musser and Ortigoza.[8] The method is based on the reduction of a phosphotungstate complex to a phosphotungstite complex with addition of hydroxylamine to intensify the color (observations are made at 660 nm).

Sodium (meq/liter)

The sodium ion content of sera is determined potentiometrically, using a sodium ion-selective glass electrode.[9]

Potassium (meq/liter)

Potassium is determined with a potassium ion-selective electrode.[10]

Carbon Dioxide (meq/liter)

The method for determining carbon dioxide is based on the automated procedure of Skeggs and Hochstrasser.[11] Carbon dioxide, released first by acid, is determined from the decrease in the red color of an alkaline phenolphthalein solution (at 550 nm).

Chloride (meq/liter)

Chloride is determined colorimetrically using the automated method of Morgenstern et al.[12] In this method, $Hg(SCN)_2$ reacts with chloride ions in the presence of ferric ions to produce red $Fe(SCN)_3$ (observed at 480 nm).

Calcium (meq/liter)

Calcium is determined compleximetrically using an alkaline solution of 8-hydroxyquinoline.[13] The complex produces a pink color with a maximum absorption at 570 nm.

Phosphorus (meq/liter)

Inorganic phosphorus is determined by the phosphomolybdate method of Daly and Ertinghausen[14] as modified for the automatic analyzer by Amador and Urban.[15] The unreduced phosphomolybdate complex absorbs at 340 nm, and the amount of phosphorus present can be determined by difference.

Na^+-(Cl^- + CO_2) (meq/liter)

Electrolyte balance is the numerical difference of Na^+ concentration and the sums of the concentrations of Cl^- and of dissolved CO_2.

Cholesterol (mg %)

Cholesterol is determined by the automated method of Levine et al.[16] In this method (based originally on that of Huang et al.[17]), cholesterol and sulfuric acid react to form bicholestadienyldisulfonic acid, a green compound measured at 630 nm in the colorimeter.

Triglycerides (mg %)

Analysis of serum triglycerides involves the enzymatic hydrolysis of the compounds to glycerol and free fatty acids.[18] A solution of glycerol kinase and pyruvate kinase in a second channel converts glycerol to pyruvate, which in turn is reduced by NADH and lactic acid dehydrogenase to lactate (followed at 340 nm).

Bilirubin (mg %)

Determination of total bilirubin in sera, like triglycerides, involves a two-channel system for analysis. The bilirubin is reacted with a caffeine-containing diluent that forms azobilirubin. This solution is then mixed with a strongly alkaline sodium potassium tartrate buffer and sulfanilic acid to yield a green complex, which can be quantitated at 600 nm against a blank channel containing all reagents except for the diazo compound.

SGOT (mu/ml)

Serum glutamic-oxaloacetic acid transaminase (SGOT) activity is measured by following the rate of change of NADH absorption at 340 nm and 37° produced by maleate dehydrogenase. The latter enzyme system is coupled with GOT-catalyzed transamination of aspartic acid and α-ketoglutaric acid in the medium.[20]

SGPT (mu/ml)

Serum glutamic-pyruvic acid transaminase (SGPT) activity is monitored in the same manner as SGOT, except that alanine is substituted for aspartic acid and the coupling enzyme is lactate dehydrogenase.[20]

LDH (mu/ml)

Lactate dehydrogenase (LDH) activity is determined directly by monitoring the rate of change in absorption at 340 nm in the presence of added L-lactic acid and NAD^+.[12]

Alkaline Phosphatase (mu/ml)

The Technicon method for determination of alkaline phosphatase involves the hydrolysis of stock p-nitrophenyl phosphate solutions by the enzyme in the presence of Mg^{2+} to produce a bright-yellow p-nitrophenol product (monitored at 410 nm and 37°) at pH 10.25.[21]

Iron (mcg %)

Serum iron (expressed as microgram %) is determined by reacting 3-(2-pyridyl)-5,6-bis-(4-phenylsulfonic acid)-1,2,4-triazine (trademarked as FerroZine) in the presence of ascorbic acid to liberate transferrin-bound iron.[22] The FerroZine complex in a sodium acetate medium is measured colorimetrically at 560 nm.

Total Protein (g %)

The method for total protein is based on the biuret method, automated for use with the Technicon analyzer.[10]

Albumin (g %)

The Technicon method utilizes the reactivity of albumin with bromcresol green (BCG) to form an albumin-BCG complex that can be quantitated colorimetrically at 630 nm.[23]

Globulin (g %)

Globulin is the difference of total protein and albumin determinations.

A/G Ratio

The albumin-to-globulin (A/G) ratio is calculated individually for each animal sample, and the ratios are averaged for each group by a computer program.

Hematology Methods - SRI

Hematological and clinical chemistry determinations on rat sera from the LAP(I) study (Part 4) were conducted in the SRI Clinical Chemistry Laboratory. The methods used in the laboratory for hematological determinations are as follows.

Erythrocyte, Leukocyte, Hematocrit, and Mean Corpuscular Volume

A Coulter electronic particle counter (Model ZBI) with a 100-μ aperture[1] is used to determine hematocrit, erythrocytes, leukocytes, and mean corpuscular volume (MCV). The instrument is standardized

daily in a two-step process as follows. The electronics is first checked for proper functioning by a standard procedure. Then the instrument is standardized for erythrocyte and leukocyte counts and for hemoglobin, hematocrit, and mean corpuscular volume against 4C normal and abnormal control standards (Coulter Electronics Inc.). Each blood sample was counted in duplicate.

Hemoglobin (Hgb)

Hemoglobin is determined in a Coulter hemoglobinometer as cyanomethemoglobin.[2] Cyanomethemoglobin standards were supplied by Coulter Electronics Inc. as part of the 4C control standard. Duplicate tests were run on each blood sample.

Mean Corpuscular Volume (MCV)

MCV is determined in the Coulter counter after (daily) standardization by the Wintrobe microhematocrit method. MCV on each test sample is determined in duplicate.

Hematocrit (Hct)

Hematocrit is calculated from the following equation:

$$\text{Hct} = \text{RBC}\ (10^6/\text{mm}^3) \times \text{MCV}\ (\mu^3) \quad .$$

Mean Corpuscular Hemoglobin (MCH)

MCH was calculated as follows:

$$\text{MCH}\ (\mu\mu\text{g}) = \frac{\text{Hgb}\ (\text{g}\ \%) \times 10}{\text{RBC}\ (10^6 \times \text{mm}^3)}$$

Mean Corpuscular Hemoglobin Concentration (MCHC)

MCHC is calculated as follows:

$$\text{MCHC}\ \%\ (\text{g}\ \%) = \frac{\text{Hgb}\ (\text{g}\ \%) \times 100}{\text{Hct}}$$

Differential Leukocyte Counts

Leukocytes are stained with Wright's stain for examination and counting under a light microscope. Cell types identified and counted are polymorphonuclear cells, band cells, lymphocytes, atypical lymphocytes, monocytes, eosinophils, and/or basophils.

Reticulocyte Count (Retic)

Reticulocytes are counted on a brilliant cresyl blue-stained differential smear under a microscope.

Heinz Bodies

Heinz bodies are stained with methyl-violet and the percentage is calculated. Heinz bodies were not reported in the text unless the test was positive.

Clinical Chemistry - SRI

The clinical chemistry tests described below were performed at SRI International on the blood samples. These tests represent a GEM 15 (GEMSAEC 15) profile as described in GEMSAEC manual (Technical Publication No. I.M. 030085, May 1976) by Electro-Nucleonics, Inc. (Fairfield, N.J.).

GEMSAEC is a computerized and automated blood analyzer system made up of five component modules. GEMSAEC performs either end-point or kinetic type analyses. The instrument centrifugally mixes reagents and clinical samples, moving the mixture through the light path of a spectrophotometer, the output of which is converted to digital data for computation in a digital minicomputer and is printed out on a teletypewriter. A small integral oscilloscope allows visual monitoring of analyses. Standardization for each test was made on every 16 samples, using Smith Kline Instruments Inc. reference sets (normal and abnormal).[24,25]

BUN (mg %)

The GEMSAEC method used for determination of BUN is a modification of the procedure described by Talke and Schubert.[26] This method of determining urea in blood involves release of ammonia from urea by the action of urease. It serves as substrate with α-keto glutarate for the enzyme glutamic dehydrogenase, forming glutamate. In this reaction, reduced nicotinamide adeninedinucleotide (NADH) is oxidized, the amount being proportional to the amount of urea in the sample. The oxidation is followed quantitatively by the decrease of absorbance at 340 nm as NAD^+ is formed from NADH.

Creatinine (mg %)

Creatinine is analyzed by the original method of Jaffe,[6] in which the creatinine is allowed to react with saturated picric acid in alkaline solution at 30° to produce a bright orange-red solution. Analysis in the colorimeter is performed at 520 nm.

Uric Acid (mg %)

For determination of uric acid in clinical specimens, uric acid is oxidized by the specific enzyme uricase to allantoin, CO_2, and H_2O_2.[27] In the presence of catalase, the H_2O_2 formed is used to oxidize methanol to formaldehyde. The formaldehyde is transformed by the Hantzsch reaction,[28] in the presence of acetylacetone and ammonia, into a yellow-colored lutidine derivative. The yellow color of this dye is directly proportional to the concentration of uric acid. The color is measured photometrically between 405 and 415 nm.

Calcium (mg %)

The GEMSAEC calcium analysis determines calcium colorimetrically, using a metal-complexing dye, cresolphthalein complex, and a diethylamine base reagent. 8-Hydroxyquinoline is present in the test to eliminate any interference due to magnesium ions. A red-purple complex forms that is proportional to the amount of calcium present.[29]

Phosphorus (mg %)

Inorganic phosphorus is determined by the phosphate ions in the serum reacting with ammonium molybdate in the presence of sulfuric acid[30] to form phosphoromolybdic acid. This is then reduced by ferrous ammonium sulfate to form a blue-colored complex with a maximum absorbance at 675 nm. The formation of the blue complex is proportional to the concentration of phosphorus in the sample.

Glucose (mg %)

Glucose reacts with adenosine triphosphate (ATP) in the presence of hexokinase with the formation of glucose-6-phosphate and adenosine diphosphate (ADP). Glucose-6-phosphate reacts with nicotinamide adenine dinucleotide (NAD^+) in the presence of glucose-6-phosphate dehydrogenase with the formation of 6-phosphogluconate and NADH. The NADH produced absorbs strongly at 340 nm.[31]

Total Bilirubin (mg %)

Determination of serum bilirubin in the GEMSAEC is effected in the presence of caffeine. Sodium benzoate bilirubin couples with diazotized sulfanilic acid to form azobilirubin, which is pink and has an absorbance maximum around 545 nm. This reaction is very rapid and is performed outside the analyzer by adding caffeine sodium benzoate to the serum. Addition of sodium-potassium tartrate changes the pH to highly alkaline and moves the absorbance maximum to 600 nm. The absorbance at 600 nm is proportional to the total bilirubin concentration in the serum.[32]

Cholesterol (mg %)

Cholesterol is determined by the automated method of Allain et al.[33] in which cholesterol esters are hydrolyzed to free cholesterol and fatty acids by cholesterol esterase. The cholesterol released by this process and that pre-existing free in the sample are then oxidized by the enzyme cholesterol oxidase. The hydrogen perioxide released in the oxidation step reacts with 4-aminoantipyrine and phenol in the presence of horseradish peroxidase. The quinone imine product is red in color, with λ_{max} at 500 nm.

Triglycerides (mg %)

Analysis for serum triglycerides involves the enzymatic hydrolysis of the compounds to glycerol and free fatty acids.[18] A solution of glycerol kinase and pyruvate kinase converts glycerol to pyruvate, which in turn is reduced by NADH and lactic dehydrogenase to lactate (followed at 340 nm).

SGOT (IU/L)

Serum glutamic-oxaloacetic acid transaminase (SGOT) activity is measured by following the rate of change of NADH absorption at 340 nm and 30° produced by malate dehydrogenase. The latter enzyme system is coupled with GOT-catalyzed transamination of aspartic acid and α-ketoglutarate in the medium.[34,35]

SGPT (IU/L)

Serum glutamic-pyruvic acid transaminase (SGPT) activity is monitored in the same manner as SGOT except that alanine is substituted for aspartic acid and the coupling enzyme is lactate dehydrogenase.[34,35]

LDH (IU/L)

Lactate dehydrogenase (LDH) activity is determined directly by monitoring the rate of change in absorption at 340 nm in the presence of added L-lactic acid and NAD^+.[12]

Alkaline Phosphatase (IU/L)

In the GEMSAEC method for determining alkaline phosphatase, *p*-nitrophenyl phosphate is used as the substrate and the enzyme acts to form *p*-nitrophenol and inorganic phosphate or mannitol phosphate as products. The released *p*-nitrophenol is in the form of the dissociated phenylate ion at the reaction pH, which form has a distinctive yellow color that absorbs light maximally at a wavelength of 405 nm.[36]

Appendix A

Total Protein (g/L)

The method for total protein is based on the biuret method, adapted for use with the GEMSAEC analyzer.[37]

Albumin (g/L)

The GEMSAEC method utilizes the reactivity of albumin with bromocresol green (BCG) to form an albumin-BCG complex that can be quantitated colorimetrically at 628 nm.[23]

Other

Globulin and albumin/globulin (A/G) ratios are not ordinarily a part of the SRI Clinical Chemistry Laboratory output with the GEMSAEC. Approximate values for each may be calculated using the total protein and albumin mean values in the clinical chemistry tables. These calculations were done by hand, but since no consistent pattern was found in the results, the computer was not reprogrammed to include these data in the tables.

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URINALYSIS

Urine samples were collected from dogs, mice, and rats at sacrifice and sent to Peninsula Medical Laboratory for analysis. The following tests or observations were made: color, specific gravity, pH, albumin, sugar, appearance, WBC, RBC, epithelial cells, casts, bacteria, and crystals. The standard methods used at Peninsula Medical Laboratory are as follows.

I. MACROSCOPIC EXAMINATION

A. Report color of sample.

1. Normally, almost colorless (straw), light yellow, yellow, dark yellow or amber.

2. Pathological sample may be red, reddish brown, milky, port wine or beer brown.

3. Non-pathological coloration from drugs and food may be red, blue, brown, green or yellow.

B. Report turbidity as:

Clear, slight, moderate, or marked.

C. Specific Gravity.

Refractometer: For samples of less than 25 ml. urine, use TS (total solids) meter. Add one drop of urine to prism allowing sample to fill space between prism and cover by capillary action. Rinse well between samples.

Read scale at the point of the dividing line between light and dark fields. Clean prism with soft cloth or tissue only. Do not immerse in water.

Normal values are 1.003-1.030.

D. pH.

1. Use Nitrazine paper and compare the color that develops to the color scale on the dispenser.

2. Normal value is 4.8-7.5.

3. Alkaline Urine
   i. Due to breakdown of urea to ammonia.
   ii. After ingestion of heavy meal.
   iii. After ingestion of alkaline drugs.

E. Sugar.

1. All samples for routine urinalysis:

   Dip Tes-Tape into urine. Read color change if any in ONE minute. Compare with color chart on dispenser and report results.

2. Normal value is a negative glucose.

3. Samples from pediatrics and nursery: (Not applicable to SRI)
   In addition to Tes-Tape, do a Clinitest.

   i. To 5 drops of urine and 10 drops of water, add 1 Clinitest tablet. Watch reaction. If color changes from orange to some shade of brown, a sugar content greater than 2% is present and should be recorded thus without reference to the color chart.

   ii. Wait 15 seconds after boiling stops; shake gently and compare with color chart.

   iii. Report Tes-Tape results in Glucose column and Clinitest results in space marked "Other".

4. Principles of Tes-Tape:

   The strip contains the enzyme glucose oxidase and a catalyst chromogen substance. When dipped in a solution of glucose, the following reaction occurs:

$$\text{Glucose} + O_2 \xrightarrow{\text{GLUCOSE OXIDASE}} \text{Gluconic acid} + H_2O_2$$

$$H_2O_2 + \text{chromogen} \xrightarrow{\text{PEROXIDASE}} \underset{\text{(green)}}{\text{Oxidized chromogen}} + H_2O$$

5. Principle of Clinitest:

This is a self heating tablet method for the determination of reducing substances. Reagents include copper sulfate, citric acid, sodium hydroxide, and sodium carbonate. Citric acid and sodium carbonate act as effervescents to aid solution of tablet and sodium hydroxide provides alkaline media. Cupric ions (++) are reduced to cuprous oxide (Cu_2O), giving a color change from blue to orange, depending on the amount of reducing substances present.

$$2\ Cu^{++} + \text{Reducing substance} \xrightarrow[\text{ALKALI}]{\text{HEAT}} Cu_2^{+}\ \text{oxidized product}$$

Sugars which reduce copper:

1. Glucose
2. Fructose
3. Lactose
4. Galactose
5. Pentose
6. Maltose

Other reducing solutions:

1. Creatinine
2. Homogentisic acid
3. Uric acid
4. Salicylates
5. Penicillin
6. Streptomycin
7. Ascorbic acid
8. Para-amino-salicylic acid

F. <u>Protein</u>.

To 5 ml. centrifuged urine sample, add 4 drops of 20% aqueous sulfosalicylic acid. Grade turbidity as follows:

Negative...no turbidity
Trace......cloudiness perceptible against black background
1+.........cloudiness distinct but not granular and barely seen when held up to light
2+.........cloud is distinct and granular when held up to light
3+.........cloud is heavy with distinct flocculi
4+.........cloud is dense with large flocculi and may precipitate completely

Normally no protein is detected in urine. Non-pathologic protein uria may be caused by:

1. Excessive exercise
2. Exposure to cold
3. Orthostatic albuminuria

Appendix A

False positive results for protein by sulfosalicylic acid method:

1. Orinase (Tolbutamide - medication for mild diabetics)
2. Penicillin - massive doses
3. Gantrisin
4. Para-aminosalicylic acid
5. X-ray contrast media

False negative results may be caused by highly buffered alkaline urine.

G. Ketone Bodies.

1. Ketostix:

   Dip test end into urine. Read in 15 seconds and compare with color chart. Positive reactions occur with 5-10 mg. % acetoacetic acid.

2. Acetone and acetoacetic acid react with sodium nitroprusside to produce a purple complex, the intensity of which is proportional to the concentration of ketones present. Acetoacetic acid is irreversibly converted to acetone upon standing. Test should therefore be done on a relatively fresh sample.

3. False positive reactions obtained in urine containing:

   i. Bromsulphalein
   ii. Phenylketones (in quantities greater than 100 mg. %).

II. MICROSCOPIC EXAMINATION

Centrifuge 10 ml. urine for 5 minutes at 3/4 speed in conical centrifuge tube. Decant all but 0.2 ml. in tube. Mix well. Concentration is now 50 X. Supernatant may be used for protein determination. Add one drop of well mixed sediment to slide and cover with cover glass.

Low power 10 X.

1. Casts: Report number and kind/low power field.

   Cellularity - WBC cast
   RBC cast
   Epithelial cast
   Hyaline cast
   Waxy cast
   Coarse granular cast
   Fine granular cast

Size - - - - Broad
Narrow
Shape - - - Report if convoluted

2. Cylindroids: Report number.

3. Mucus threads: Report as few, moderate, many.

4. Epithelial Cells: Report kind - squamous, round, caudate. Report amount - few, moderate, many.

5. <u>Crystals</u>.

Acid urine:

A. Uric acid
B. Calcium oxalate
C. Amorphous urates (dissolves with heat)
D. Others

Alkaline urine:

A. Triple phosphates
B. Calcium phosphate
C. Calcium carbonate
D. Ammonium urate
E. Amorphous phosphates (dissolves in acetic acid)

Report as few, moderate, or many in low power field. Identify crystals under high power.

High power 45 X

Report number/high power field.

1. WBC
2. RBC
3. WBC clumps
4. Yeast
5. Trichomonads
6. Spermatozoa

Report bacteria as few, moderate, or many.

STATISTICAL METHODS

A common tabular format has been developed to allow a rapid comparison of group results from toxicologic studies. For the majority of the parameters measured in such studies (body weights, weight gains, organ weights, hematology, and clinical chemistry), the tables contain the mean parameter value for each treatment group along with the standard error of the mean and the number of animals in the group. For food consumption (which is measured on a cage basis rather than on an animal basis), the tables contain the mean food consumption for each treatment group and the number of animals in the group. The tables compactly display a large portion of the quantitative data gathered in the study (aside from observations made during the study on animal appearance and behavior and during necropsy on abnormalities).

Statistical procedures have been applied to the data in the tables to aid the investigator in identifying the significant results (that is, difference in mean parameter values that would be unlikely to have resulted from natural biological variability).

In this study on TNT wastewaters, the statistical tests were applied to the data on body weights, weight gains, organ weights, hematology, and blood chemistry whenever the group size was three or larger. The statistical tests were not applied when the group size was one or two animals, since the tests depend on the approximate normality of the distribution of the mean and these sample sizes were judged too small to give reasonable assurance of this normality.

To permit easy identification of the statistically significant results and to form a visual pattern that will naturally lead the investigator's attention to clusters of significant results, the significance of these statistical tests is denoted by the use of symbols (+, *) and letters (A, B, C, D) placed on the same tables as the means, standard errors, and group sizes.

The first statistical test is Bartlett's chi-square test.* This test examines the variances of the treatment and control groups and flags the condition of unequal variances. If Bartlett's chi-square test is not significant at the 5% level, no symbol is printed in the B column. The symbol * denotes that the test is significant at the 5% level and the symbol + denotes that the test is significant at the 1% level. The primary use of Bartlett's chi-square test is in the selection of the proper statistical tests for examination of the means of the treatment and control groups.

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* K. A. Brownlee. Statistical Theory and Methodology in Science and Engineering. John Wiley and Sons, New York, c. 1960, pp. 225-226.

Next each treatment mean is examined to determine whether it is significantly larger or smaller than the control mean. If the Bartlett's chi-square test is not significant at the 5% level, the statistic used for this comparison is a t-statistic computed with a pooled variance estimate. This statistic is compared with a Scheffe multiple comparison cutoff value for contrasts to determine its significance. The pooled variance estimate is derived using all the groups. This test is known as Scheffe's test* and, as a simultaneous statistical procedure, guarantees a significance level of 5% or 1% over all the treatment-control comparisons. If Bartlett's chi-square test is significant at the 5% (or 1%) level, the statistic used for the treatment-control comparison is a t-statistic computed with separate group variance estimates. This statistic is compared with a Student's t-cutoff value. This t-test is not a simultaneous test. On the basis of Bartlett's chi-square test, the computer automatically decides which treatment-control comparison to compute. In either case, a result significant at the 5% level is denoted in the T column by a * and a result significant at the 1% level is denoted by a +.

While the t- and Scheffe tests assess whether the treatment and control means are significantly different, Finney's ratio test† assesses the magnitude of that difference. Finney's ratio test is a procedure for examining the ratio of each dose group mean to the control group mean, while taking into account the variability demonstrated in the data. In particular, this test is used to form a 95% confidence interval for the ratio of a dose group mean to the control mean. If the confidence interval lies entirely above 1.10 or below 0.90, the symbol A is printed. If the confidence interval lies entirely above 1.20 or below 0.80, the symbol B is printed. The symbol C corresponds to an interval above 1.35 or below 0.65 and the symbol D corresponds to values of 1.50 and 0.50. Thus, using Finney's ratio test, if the letter D were printed, we might be able to say that we are 95% confident that at the highest dose level the mean response is at least 150% of the control group mean response. The computer program automatically uses either separate or pooled variance estimates in Finney's ratio test, depending on whether Bartlett's chi-square test is significant. The ratio test is not a simultaneous test statistic in either case, however. The symbol x is printed if the ratio test cannot be computed.

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* A. Scheffe. The Analysis of Variance. John Wiley and Sons, New York, 1959, pp. 20-21.

† D. J. Finney. Probit Analysis. Cambridge University Press, England, 1971, pp. 76-80.

PATHOLOGY

Euthanasia

Dogs are anesthetized with T61 or sodium pentobarbital intravenously; then they are exsanguinated. Rats and mice receive sodium pentobarbital intraperitoneally.

Postmortem (Gross) Examination

External

The physical condition of the animal is observed and recorded. Lesions are sought in skin, eyes, and other structures in which they are externally evident. The nature and quantity of discharges from any of the body openings are also noted.

Internal

The carcass is opened systematically, starting anteriorly and proceeding caudally. The brain is removed first, followed by the eyes. Neck organs, thoracic, abdominal and pelvic viscera are observed in situ and removed. Hollow viscera are opened and examined grossly. Solid viscera are carefully sliced and examined. All abnormalities are described. Specimens $\leq$ 5 mm thick are placed in neutral buffered formalin for not less than 3 days.

Organ Weights

Specified organs are trimmed, each in a routine manner, and the weights are recorded. Fluid is released from cholecyst for liver weight, and in the case of large animals the heart is opened for release of unclotted blood or removal of clots before it is weighed. The ratio of organ weight to body weight and to brain weight is determined.

Microscopic Examination

Specified fixed tissues and lesions that always include some adjacent normal tissue are processed to H & E slides for histopathologic evaluation. If, in the judgment of the pathologist, special stains are required, they are requested.

Reports include individual findings, group incidences, intergroup comparisons, and determinations of spontaneity or relationship to experimental treatment.

Appendix B

CALCULATIONS, STANDARDS, AND BACKGROUND DATA

WORK SHEET FOR LD_{50} CALCULATIONS (THOMPSON and WEIL)*

Compound No. TNT Date Intubated ______

Mode RAT ♂ Date of Calculation 6-3-75

n = 10 r values = 0 (500), 5 (1000), 6 (2000), 10 (4000)

f = .4 σf = .23336

Lowest dose (Da) = 500 mg/kg log Da = 2.69897

Dosage ratio = 2 d = log dosage ratio = .30103

log m = log Da + [d . (f + 1)]

=

=

= 3.12041

anti log of log m = 1319.5

95% Confidence limits = log m ± 2d · σf

2d · σf =

=

=

log m ______ + ______ = 3.26091 = anti log = 1823.5

log m ______ - ______ = 2.97992 = anti log = 954.8

LD_{50} and 95% Confidence Limits = 1,320 (955 - 1,824) mg/kg

* C. S. Weil. Tables for convenient calculation of median-effective dose (LD50 or ED50) and instructions in their use. Biometrics 8, 249-263 (1952).

Project No. 5028-1

WORK SHEET FOR LD_{50} CALCULATIONS (THOMPSON and WEIL)

Compound No. TNT Date Intubated ____

Code RAT ♀ Date of Calculation 6-3-76

n = 10 r values = 0 (250), 1 (500), 8 (1000), 9 (2000)

f = 0.66667 σf = 0.19945

Lowest dose (Da) = 250 mg/kg log Da = 2.39794

Dosage ratio = 2 d = log dosage ratio = .30103

log m = log Da + [d . (f + 1)]

= 2.89966

=

=

anti log of log m ____ = 793.7

95% Confidence limits = log m ± 2d $\cdot \sigma f$

2d $\cdot \sigma f$ =

=

= .12008

log m ____ + ____ = 3.01974 = anti log = 1046.5

log m ____ - ____ = 2.77958 = anti log = 601.9

LD_{50} and 95% Confidence Limits = 794 (602 - 1047) mg/kg

Project No. 5078-1

SRI - CHEMICAL AND ENVIRONMENTAL TOXICOLOGY

WORK SHEET FOR LD_{50} CALCULATIONS (THOMPSON and WEIL)

Compound No. TNT Date Intubated

Code Mouse ♀ Date of Calculation 6-3-76

n = 10 r values = 0 (250), 1 (500), 10 (1000), 10 (2000)

f = 0.4 σf = .1

Lowest dose (Da) = 250 mg/kg log Da = 2.39794

Dosage ratio = 2 d = log dosage ratio = .30103

log m = log Da + [d . (f + 1)]

=

=

= 2.81938

anti log of log m = 659.75

95% Confidence limits = log m ± 2d • σf

2d • σf = .06021

=

=

log m + = 2.87959 = anti log = 757.9

log m - = 2.75918 = anti log = 574.3

LD_{50} and 95% Confidence Limits = 660 (574 - 758) mg/kg

Project No.

WORK SHEET FOR LD_{50} CALCULATIONS (THOMPSON and WEIL)

Compound No. TNT Date Intubated

Code mouse ♂ Date of Calculation 6-3-76

n = 10 r values = 0 (250), 2 (500), 9 (1000), 10 (2000)

f = 0.4 σf = 0.16667

Lowest dose (Da) = 250 mg/kg log Da = 2.398

Dosage ratio = 2 d = log dosage ratio = .30103

log m = log Da + [d . (f + 1)]

= 2.398 + [.30103 (0.4 + 1)]

=

= 2.8194

anti log of log m = 659.75 mg/kg

95% Confidence limits = log m ± 2d · σf

2d · σf = .100345

=

=

log m 2.8194 + = 2.9197 = anti log = 831.3

log m 2.8194 - = 2.71905 = anti log = 523.7

LD_{50} and 95% Confidence Limits = 660 (524 - 831) mg/kg

Project No. 5028-1

C 5028-1 LD50 RDX RATS-MALE ENTRY:SG 7/11/78
FUNCTION OF DOSE -- NATURAL LOG

DOSE	NUMBER	MORTALITY	PERCENT MORTALITY	WEIGHT COEFF	PROBIT	WORKING PROBIT	CONTRIBUTION TO CHI-SQUARE
.250000E+02	10.	0.	0.0000	.312881E-01	-2.6981	-3.0341	.353143E-01
.500000E+02	10.	0.	0.0000	.469852E+00	-.9048	-1.5948	.223688E+01
.750000E+02	10.	7.	.7000	.631830E+00	.1442	.5055	.825043E+00
.100000E+03	10.	10.	1.0000	.475190E+00	.8885	1.5845	.230189E+01
.150000E+03	10.	10.	1.0000	.145334E+00	1.9375	2.3690	.270659E+00
.200000E+03	10.	9.	.9000	.326549E-01	2.6817	-6.1176	.252841E+02
.250000E+03	10.	10.	1.0000	.580000E-02	3.2590	3.2590	0.

0 SLOPE = .258635E+01 INTERCEPT = -.110225E+02 ITERATION NUMBER 4

LD50	SE(LD50)	PERCENT ERROR(LD50)	SLOPE	SE(SLOPE)	PERCENT ERROR(SLOPE)
.709371E+02	.664483E+01	9.37	.258635E+01	.617214E+00	23.86

CHI-SQUARE	DEGREES OF FREEDOM	PROBABILITY OF POOR FIT	G(95 PERCENT CI)
.309539E+02	5	.998000E+00	.218780E+00

LD50 70.937084

95 PERCENT
CONFIDENCE 56.225671 AND 85.361851
LIMITS
1
EXIT
/

C5028-1 LD50 RDX RAT-FEMALE ENTRY:SG 7/11/78

1 PARTIAL RESPONSE - DATA SET REJECTED

DOSE	NUMBER	MORTALITY
25.00	10.	0.
50.00	10.	0.
75.00	10.	9.
100.00	10.	10.
150.00	10.	10.
200.00	10.	10.
250.00	10.	10.

1
EXIT
/

LD50 not computed.

1
C 5028-1 LD50 RDX MICE-MALE ENTRY:SG 7/11/78
FUNCTION OF DOSE -- NATURAL LOG

DOSE	NUMBER	MORTALITY	PERCENT MORTALITY	WEIGHT COEFF	PROBIT	WORKING PROBIT	CONTRIBUTION TO CHI-SQUARE
.750000E+02	10.	7.	.7000	.626040E+00	.2148	.5096	.544161E+00
.100000E+03	10.	6.	.6000	.606909E+00	.3621	.2514	.744598E-01
.150000E+03	10.	6.	.6000	.565262E+00	.5698	.2289	.656959E+00
.200000E+03	10.	6.	.6000	.526738E+00	.7171	.1877	.147616E+01
.250000E+03	10.	10.	1.0000	.492963E+00	.8314	1.5590	.254556E+01

0 SLOPE = .512276E+00 INTERCEPT = -.199702E+01 ITERATION NUMBER 5

LD50	SE(LD50)	PERCENT ERROR(LD50)	SLOPE	SE(SLOPE)	PERCENT ERROR(SLOPE)
.493200E+02	.523275E+02	106.10	.512276E+00	.428108E+00	83.57

CHI-SQUARE	DEGREES OF FREEDOM	PROBABILITY OF POOR FIT	G(95 PERCENT CI)
.529730E+01	3	.844720E+00	.268293E+01

LD50 49.319951

95 PERCENT
CONFIDENCE 561.637603 AND 109.863511
LIMITS
1
EXIT
/

LD50 not computed.

```
C 5028-1 LD50\MICE-FEMALE ENTRY:SG 7/11/78
FUNCTION OF DOSE  -- NATURAL LOG
    DOSE        NUMBER  MORTALITY   PERCENT    WEIGHT COEFF     PROBIT   WORKING PROBIT   CONTRIBUTION TO
                                   MORTALITY                                                CHI-SQUARE
  .750000E+02    10.       4.       .4000     .631900E+00     -.1431        -.2522         .752051E-01
  .100000E+03    10.       6.       .6000     .631054E+00      .1555         .2524         .593048E-01
  .150000E+03    10.       8.       .8000     .563630E+00      .5763         .8196         .333625E+00
  .200000E+03    10.       7.       .7000     .479492E+00      .8749         .4734         .772964E+00
  .250000E+03    10.       9.       .9000     .402448E+00     1.1066        1.2650         .100957E+00
0   SLOPE =    .103844E+01    INTERCEPT =  -.462661E+01    ITERATION NUMBER  2

  LD50           SE(LD50)    PERCENT ERROR(LD50)  SLOPE          SE(SLOPE)   PERCENT ERROR(SLOPE)
  .860872E+02    .226079E+02        26.26        .103844E+01    .444235E+00        42.78

 CHI-SQUARE    DEGREES OF FREEDOM   PROBABILITY OF POOR FIT        G(95 PERCENT CI)
  .134206E+01           3                 .279382E+00                .703038E+00


 LD50                 86.087180


 95 PERCENT
 CONFIDENCE            7.945038    AND        124.148609
 LIMITS
EXIT
/
```

C 5028 I TNT/RDX LD50 RAT MALE ENTRY:SG 8/8/78
FUNCTION OF DOSE -- NATURAL LOG

DOSE	NUMBER	MORTALITY	PERCENT MORTALITY	WEIGHT COEFF	PROBIT	WORKING PROBIT	CONTRIBUTION TO CHI-SQUARE
.234000E+03	10.	0.	0.0000	.311849E-01	-2.6994	-3.0353	.351843E-01
.351000E+03	10.	1.	.1000	.275743E+00	-1.4798	-1.2597	.144700E+00
.527000E+03	9.	3.	.3333	.621461E+00	-.2574	-.4260	.159045E+00
.650000E+03	10.	6.	.6000	.605018E+00	.3736	.2510	.909492E-01
.790000E+03	10.	10.	1.0000	.451884E+00	.9603	1.6293	.202549E+01
.900000E+03	10.	8.	.8000	.318069E+00	1.3524	.6526	.155771E+01
.119000E+04	10.	10.	1.0000	.929106E-01	2.1925	2.5862	.144045E+00

0 SLOPE = .300900E+01 INTERCEPT = -.191153E+02 ITERATION NUMBER 4

LD50	SE(LD50)	PERCENT ERROR(LD50)	SLOPE	SE(SLOPE)	PERCENT ERROR(SLOPE)
.574046E+03	.411453E+02	7.17	.300900E+01	.639481E+00	21.25

CHI-SQUARE	DEGREES OF FREEDOM	PROBABILITY OF POOR FIT	G(95 PERCENT CI)
.415713E+01	5	.472839E+00	.173509E+00

LD50 574.046230

95 PERCENT
CONFIDENCE 481.731009 AND 657.653586
LIMITS

EXIT

```
C 5028 I   TNT/RDX LD50 RAT FEMALE ENTRY:SG 6/8/78
FUNCTION OF DOSE  -- NATURAL LOG
```

DOSE	NUMBER	MORTALITY	PERCENT MORTALITY	WEIGHT COEFF	PROBIT	WORKING PROBIT	CONTRIBUTION TO CHI-SQUARE
.234000E+03	10.	0.	0.0000	.232169E-01	-2.8250	-3.1435	.235506E-01
.351000E+03	10.	1.	.1000	.238957E+00	-1.5954	-1.1954	.382452E+00
.527000E+03	10.	2.	.2000	.606779E+00	[illegible]	-.7868	.108990E+01
.650000E+03	10.	7.	.7000	.619555E+00	.2732	.5135	.357607E+00
.790000E+03	10.	9.	.9000	.482686E+00	.8647	1.2056	.560958E+00
.900000E+03	10.	8.	.8000	.349716E+00	1.2600	.7266	.995041E+00
.119000E+04	10.	10.	1.0000	.108932E+00	2.1071	2.5120	.178595E+00

```
0   SLOPE =    .303544E+01    INTERCEPT =  -.193364E+02    ITERATION NUMBER  3
```

LD50	SE(LD50)	PERCENT ERROR(LD50)	SLOPE	SE(SLOPE)	PERCENT ERROR(SLOPE)
.593887E+03	.410145E+02	6.91	.303544E+01	.650044E+00	21.42

CHI-SQUARE	DEGREES OF FREEDOM	PROBABILITY OF POOR FIT	C(95 PERCENT CI)
.358834E+01	5	.339354E+00	.176179E+03

```
LD50                593.887106

95 PERCENT
CONFIDENCE          502.467401    AND       678.259184
LIMITS
!
EXIT
/
```

```
C 5028 I TNT RDX LD50 MICE MALE ENTRY: SC 2/8/78
FUNCTION OF DOSE  -- NATURAL LOG
   DOSE        NUMBER  MORTALITY  PERCENT    WEIGHT COEFF     PROBIT    WORKING PROBIT   CONTRIBUTION TO
                                  MORTALITY                                                CHI-SQUARE
 .175000E+03    10.       0.       0.0000    0.              -5.5530      -5.5530        0.
 .790000E+03    10.       3.        .3000     .557263E+00     -.6023       -.5227         .353056E-01
 .119000E+04    20.      15.        .7500     .514930E+00      .7586        .6718         .777323E-01
 .176000E+04    10.      10.       1.0000     .110870E+00     2.0963       2.5035         .183601E+00
C  SLOPE =  .332212E+01   INTERCEPT =  -.227576E+02   ITERATION NUMBER  5

  LD50           SF(LD50)    PERCENT ERROR(LD50)  SLOPE          SF(SLOPE)   PERCENT ERROR(SLOPE)
 .947039E+03    .779313E+02       8.23           .332212E+01    .104462E+01        31.44

 CHI-SQUARE    DEGREES OF FREEDOM   PROBABILITY OF POOR FIT         G(95 PERCENT CI)
 .295839E+00          2                  .134963E+00                  .379835E+00


LD50             947.039153


95 PERCENT
CONFIDENCE       707.805018    AND      1093.633948
LIMITS

EXIT
```

```
C 5028 I TNT/RDX LD50 MICF FFMALF ENTRY: SG 8/8/78
FUNCTION OF DOSF  -- NATURAL LOG
    DOSF        NUMBFR  MORTALITY    PFRCFNT    WFICHT CCFFF     PROBIT   WORKING PROBIT   CONTRIBUTION TO
                                    MORTALITY                                              CHI-SQUARF
  .178000F+03    10.       0.        0.0000    0.                -7.7059      -7.7059      0.
  .790000F+03    10.       1.         .1000     .270964F+00      -1.4942      -1.2458       .167170F+00
  .119000F+04    10.       5.         .5000     .626176F+00        .2134       -.0034       .294146F+00
  .178000F+04    10.      10.        1.0000     .156306F+00       1.8917       2.3310       .301606F+00
   SLOPF =   .416945F+01   INTFRCFPT =  -.293131F+02   ITFRATION NUMBFR  5

  LD50          SF(LD50)    PFRCFNT FRROR(LD50)   SLOPF          SF(SLOPF)   PFRCFNT FRROR(SLOPF)
  .113055F+04   .836385F+02         7.40          .416945F+01    .120713F+01        28.95

 CHI-SQUARF    DFGRFFS OF FRFFDOM   PROBABILITY OF POOR FIT        G(95 PFRCFNT CI)
  .762921F+00           2                 .311690F+00                .322007F+00

LD50           1130.551316

95 PFRCFNT
CONFIDFNCF        945.612399    AND     1344.466924
LIMITS

FXIT
```

C5028-1 LD50 TNT/RDX RAT-MALE ENTRY:SG 7/11/78

FUNCTION OF DOSE -- NATURAL LOG

DOSE	NUMBER	MORTALITY	PERCENT MORTALITY	WEIGHT COEFF	PROBIT	WORKING PROBIT	CONTRIBUTION TO CHI-SQUARE
.300000E+03	10.	0.	0.0000	.633941E+00	.1077	-1.2610	.118762E+02
.300000E+03	10.	7.	.7000	.633941E+00	.1077	.5038	.994755E+00
.350000E+03	10.	9.	.9000	.606269E+00	.3660	1.0553	.288057E+01
.400000E+03	10.	9.	.9000	.560384E+00	.5898	1.1197	.157392E+01
.450000E+03	10.	9.	.9000	.506412E+00	.7872	1.1822	.790473E+00
.600000E+03	10.	8.	.8000	.346576E+00	1.2692	.7203	.104427E+01
.750000E+03	10.	9.	.9000	.224407E+00	1.6432	1.1615	.520610E+00

0 SLOPE = .167594E+01 INTERCEPT = -.945154E+01 ITERATION NUMBER 4

LD50	SE(LD50)	PERCENT ERROR(LD50)	SLOPE	SE(SLOPE)	PERCENT ERROR(SLOPE)
.281333E+03	.438197E+02	15.58	.167594E+01	.613935E+00	36.63

CHI-SQUARE	DEGREES OF FREEDOM	PROBABILITY OF POOR FIT	G(95 PERCENT CI)
.196808E+02	5	.997258E+00	.515512E+00

LD50 281.333227

95 PERCENT
CONFIDENCE 114.599105 AND 347.936772
LIMITS

1

EXIT

/

C 5028-1 TNT/RDX RAT-FEMALE ENTRY:SG 7/11/78
FUNCTION OF DOSE -- NATURAL LOG

DOSE	NUMBER	MORTALITY	PERCENT MORTALITY	WEIGHT COEFF	PROBIT	WORKING PROBIT	CONTRIBUTION TO CHI-SQUARE
.300000E+03	10.	0.	0.0000	.632082E+00	-.1404	-1.2647	.799023E+01
.300000E+03	10.	5.	.5000	.632082E+00	-.1404	.0010	.126378E+00
.350000E+03	10.	10.	1.0000	.621509E+00	.2570	1.2896	.662722E+01
.400000E+03	10.	8.	.8000	.557526E+00	.6012	.8231	.274512E+00
.450000E+03	10.	9.	.9000	.469844E+00	.9046	1.2174	.458858E+00
.600000E+03	10.	8.	.8000	.223372E+00	1.6465	.1868	.475932E+01
.750000E+03	10.	10.	1.0000	.881072E-01	2.2217	2.6106	.133239E+00

0 SLOPE = .257567E+01 INTERCEPT = -.148312E+02 ITERATION NUMBER 4

LD50	SE(LD50)	PERCENT ERROR(LD50)	SLOPE	SE(SLOPE)	PERCENT ERROR(SLOPE)
.316778E+03	.261543E+02	8.26	.257567E+01	.755736E+00	29.34

CHI-SQUARE	DEGREES OF FREEDOM	PROBABILITY OF POOR FIT	G(95 PERCENT CI)
.203698E+02	5	.997508E+00	.330729E+00

LD50 316.777758

95 PERCENT CONFIDENCE LIMITS 237.041064 AND 362.431124

1
EXIT
/

```
C 5028-1 LD50 TNT/RDX MICE-MALE ENTRY:SG 7/11/78
FUNCTION OF DOSE  -- NATURAL LOG
     95 PERCENT CONFIDENCE LIMITS CANNOT BE CALCULATED
    DOSE       NUMBER  MORTALITY   PERCENT   WEIGHT COEFF    PROBIT   WORKING PROBIT   CONTRIBUTION TO
                                  MORTALITY                                             CHI-SQUARE
  .300000E+03   10.       3.        .3000     .578947E+00    -.5096       -.5243        .124359E-02
  .450000E+03   10.       5.        .5000     .607583E+00    -.3579        .0157        .848011E+00
  .600000E+03   10.       1.        .1000     .622273E+00    -.2502      -1.0293        .377652E+01
  .750000E+03   10.       6.        .6000     .630223E+00    -.1667        .2558        .112495E+01
0   SLOPE =    .374196E+00   INTERCEPT =  -.264394E+01   ITERATION NUMBER  3

  LD50          SE(LD50)    PERCENT ERROR(LD50)  SLOPE         SE(SLOPE)   PERCENT ERROR(SLOPE)
  .117105E+04    .236589E+04        202.03        .374196E+00   .595410E+00       159.12

 CHI-SQUARE    DEGREES OF FREEDOM   PROBABILITY OF POOR FIT        G(95 PERCENT CI)
  .575073E+01          2                 .927710E+00                   .972626E+01


LD50              1171.04981!


95 PERCENT
CONFIDENCE          1.000000    AND         1.000000
LIMITS
1
EXIT
/
```

C 5028-1 LD50 TNT/RDX MICE-FEMALE ENTRY:SG 7/11/78

1 PARTIAL RESPONSE - DATA SET REJECTED

DOSE	NUMBER	MORTALITY
300.00	10.	0.
450.00	10.	4.
600.00	10.	1.
750.00	10.	4.

1
EXIT
/

LD50 not computed.

```
C 5028 I IRRADIATED TNT/RDX LD50 HALF ENTRY: SG 8/8/78
FUNCTION OF DOSE  -- NATURAL LOG
   DOSE        NUMBER  MORTALITY   PERCENT    WEIGHT COEFF    PROBIT   WORKING PROBIT   CONTRIBUTION TO
                                   MORTALITY                                             CHI-SQUARE
 .100000E+01    10.       9.        .9000     .224418E+00     1.6431      1.1615        .520499E+00
 .750000E+00    10.       8.        .8000     .514199E+00      .7612       .8390        .311812E-01
 .600000E+00    10.       7.        .7000     .635250E+00      .0771       .5026        .115055E+01
 .500000E+00    10.       2.        .2000     .534808E+00     -.4819      -.8055        .612291E+00
 .250000E+00    10.       0.       0.0000     .391934E-01    -2.6069     -2.9439        .458269E-01
0  SLOPE =   .306554E+01   INTERCEPT =   .164286E+01   ITERATION NUMBER  3

  LD50          SF(LD50)    PERCENT ERROR(LD50)  SLOPE          SF(SLOPE)    PERCENT ERROR(SLOPE)
 .585135E+00   .442994E-01        7.57          .306554E+01    .877977E+00        28.64

 CHI-SQUARE    DEGREES OF FREEDOM   PROBABILITY OF POOR FIT         G(95 PERCENT CI)
 .236035E+01           3               .496509E+00                   .315112E+00

LD50                 .585135

95 PERCENT
CONFIDENCE           .472473    AND        .679859
LIMITS
I
EXIT
/
```

```
C 502F 1 IRRADIATFD TNT/RDX LD50 FFMALF FNTRY:SG 8/3/78
FUNCTION OF DOSF  -- NATURAL LOG
    DOSE        NUMBFR  MORTALITY   PFRCFNT    WFIGHT COFFF     PROBIT    WORKING PROBIT   CONTRIBUTION TO
                                   MORTALITY                                                 CHI-SQUARE
  .100000F+01    10.       9.        .9000     .438494E+00     1.0001        1.2426        .257873F+00
  .750000F+00    10.       5.        .5000     .623091E+00      .2428        -.0048         .381933F+00
  .600000F+00    10.       3.        .3000     .609656F+00     -.3446        -.5180         .183415F+00
  .500000F+00    10.       3.        .3000     .495125F+00     -.8245        -.4894         .555991F+00
  .250000F+00    10.       0.       0.0000     .357054F-01    -2.6491       -2.9649         .402486F-01
0  SLOPF =   .263306F+01   INTFRCFPT =   .100050F+01   ITFRATION NUMBFR  3

  LD50           SF(LD50)     PFRCFNT FRROR(LD50)   SLOPE          SF(SLOPF)    PFRCFNT FRROR(SLOPE)
  .683877F+00    .555765F-01        8.13           .263305F+01    .783773F+00        29.77

 CHI-SQUARE     DEGRFFS OF FRFFDOM    PROBABILITY OF POOR FIT          G(95 PFRCFNT CI)
  .141946E+01          3                   .297445F+00                   .340385F+00


 LD50                 .683577


 95 PFRCFNT
 CONFIDFNCF           .568213    AND        .841274
 LIMITS
1
FXIT
/
```

PRECISION OF HEMATOLOGY AND CLINICAL CHEMISTRY TESTS

Peninsula Medical Laboratory, a fully state-accredited clinical test laboratory in Menlo Park, California, performed daily standardization tests for hematology and clinical chemistry before and during examination of the test samples. Records of these daily standardization tests were not supplied.

PML subscribes to the Proficiency Test Service conducted by the American Society of Internal Medicine (205 W. Levee Street, Brownsville, Texas 78520). Quarterly, this service sends PML samples of two different sera or solutions for hematological and clinical chemistry analyses. When returned to American Society of Internal Medicine, the results are compiled and statistically analyzed for all the participants in the service. A report of the results of the survey are returned to PML within 15 days after submission. Tables B-1 and B-2 summarize the hematological and clinical chemistry results of PML's participation in this service for the period covering the subacute studies on TNT and LAP. PML is also tested quarterly by this service for urinalysis. The results of these tests for the same period are too voluminous to summarize here but will be forwarded with raw data on the studies in this volume to USAMRDC.

Appendix B

Table B-1

PROFICIENCY TEST SERVICE REPORTS (1976-77)[a]
ON HEMATOLOGY VALUES[b] FROM PENINSULA MEDICAL LABORATORY

Parameter	PML	Reference[c]	All Participants[d]
RBC (x 10^6)	3.25	3.19	3.20 ± 0.11
Hgb (g %)	9.55	9.55	9.58 ± 0.25
Hct (%)	21.1	21.7	21.7 ± 1.07
WBC (x 10^3)	10.7	10.4	10.5 ± 0.51
Segmented (%)	57.4	54.6	54.6 ± 5.9
Band (%)	5.44	5.59	5.59 ± 3.9
Lymphocytes (%)	28.9	21.6	21.6 ± 6.3
Atyp. Lymp. (%)	4.0	4.8	4.8 ± 2.5
Monocytes (%)	3.11	3.42	3.42 ± 1.89
Eosinophils (%)	9.33	8.40	8.40 ± 2.33

[a]An average of five quarterly results reports spanning the last quarter of 1976 and all of 1977.

[b]Means are reported.

[c]American Society of Internal Medicine means.

[d]Means ± standard deviations.

Table B-2

PROFICIENCY TEST SERVICE REPORTS (1976-77)[a]
ON CLINICAL CHEMISTRY VALUES FROM PENI LA MEDICAL LABORATORY

Parameter	Values[b] PML	Reference[c]	All Participants[d]
Albumin (g %)	3.30	3.30	3.88 ± 0.27
Alk-P	2.54	2.37	2.38 ± 0.52
Bilirubin (mg %)	2.33	2.24	2.35 ± 0.33
Ca^{2+} (mg %)	9.37	9.48	9.52 ± 0.44
Cl^- (meq/l)	93.2	99.4	100.3 ± 3.3
Cholesterol (mg %)	132	132	132 ± 15
Creatinine (mg %)	3.21	2.85	2.98 ± 0.26
Glucose (mg %)	97.9	104.6	102.2 ± 8.7
Fe (mcg %)	121	108	111 ± 12
LDH	1.73	1.75	1.74 ± 0.19
P (mg %)	4.82	5.15	5.15 ± 0.35
K^+ (meq/l)	3.90	3.96	3.99 ± 0.11
Protein (g %)	5.91	6.00	6.02 ± 0.19
Na^+ (meq/l)	130	133	133 ± 2.8
SGOT	1.65	1.71	1.72 ± 0.31
SGPT	1.36	1.45	1.43 ± 0.30
Triglycerides	59.7	75.4	85.1 ± 24.6
BUN (mg %)	21.6	21.4	21.4 ± 1.6
Uric acid (mg %)	6.44	6.85	6.85 ± 0.75

[a]An average of five quarterly results reports spanning the last quarter of 1976 and all of 1977.

[b]Means are reported.

[c]American Society of Industrial Medicine means.

[d]Means ± standard deviations.

BACKGROUND DATA

Background data on dogs, rats, and mice are normal values for control animals as determined in these and other studies. Several sources of information are available for deriving normal ranges of values for body weights, hematology, and clinical chemistry. Marshall Laboratory Animals supplied us with the hematology and clinical chemistry determinations made on their beagles by other customers. Tables B-3 and B-4 summarize these values.

We have conducted a number of subacute studies for other clients with Sprague-Dawley rats. Tables B-5 and B-6 present the range of values obtained for the controls in these studies. (Hematology and clinical chemistry determinations were conducted at Peninsula Medical Laboratory.)

In the studies for USAMRDC, we pooled control data on body weights, organ weights, hematology, and clinical chemistry for dogs, rats, and mice for reference (Tables B-7 through B-12). These data are most appropriate for providing the normal range of values for comparisons with treatment means since these controls span the period of testing for USAMRDC and the same analytical methods are used on these animals.

Appendix B

Table B-3

HEMATOLOGY OF BEAGLES FROM MARSHALL LABORATORY ANIMALS*

Parameter	Values† Males	Values† Females
Hgb (g %)	15.6 ± 1.9	16.3 ± 2.2
Hct (%)	45.4 ± 5.6	47.9 ± 4.4
WBC (x 10^3)	15.0 ± 3.7	13.7 ± 3.4
PMN (%)	60.6 ± 12.8	61.8 ± 8.8
Lymphocytes (%)	33.7 ± 7.6	34.8 ± 8.4
Monocytes (%)	1.3 ± 1.2	1.1 ± 1.2
Eosinophils (%)	2.5 ± 2.7	2.1 ± 3.0
Basophils (%)	0.08 ± 0.35	0.045 ± 0.3
Retic (% x 1000 RBC)	0.37 ± 0.36	0.42 ± 0.40

* Values are derived from averages for 100 male or 100 female dogs (age, 9 to 12 months) supplied to Marshall Research on its beagles by customers.

† Means ± standard error.

Table B-4

CLINICAL CHEMISTRY OF BEAGLES FROM MARSHALL LABORATORY ANIMALS[a]

Parameter	Males	Females
Glucose (mg %)	80 ± 7.6	76.5 ± 10.4
BUN (mg %)	15.9 ± 4.0	17.8 ± 4.3
Serum Na+ (meq/liter)	149.8 ± 12.4	149.1 ± 16.7
Serum K+ (meq/liter)	4.9 ± 0.48	4.8 ± 0.49
SGOT (Wrobl. units)	16.4 ± 13.1	16.7 ± 13.4
SGPT (Wrobl. units)	10.4 ± 9.1	11.5 ± 7.5
Alk-P (Bessy-Lowry units)	2.8 ± 1.0	2.4 ± 1.2
Serum protein (mg %)	6.0 ± 0.62	6.1 ± 0.70

[a]Values are derived from averages for 100 male or 100 female dogs (age, 9 to 12 mo) supplied to Marshall Research on its beagles by customer.

[b]Means ± standard error.

Table B-5

RANGE OF HEMATOLOGY VALUES IN RATS*

Parameter	Range of Values: Males	Range of Values: Females
RBC (x 10^6)	5.44 - 8.35	6.06 - 7.87
Hgb (g %)	12.0 - 14.8	12.3 - 15.2
Hct (%)	36.1 - 42.8	37.2 - 43.1
MCV $(\mu)^3$	48 - 68	50 - 64
MCH (μμg)	16.8 - 22.0	18.3 - 20.4
MCHC (%)	33.0 - 35.7	32.3 - 35.5
WBC (x 10^3)	6.2 - 15.1	5.5 - 14.5
Neutrophils (%)	7 - 27	3 - 35
Bands (%)	0	0
Lymphocytes (%)	70 - 92	58 - 95
Monocytes (%)	0 - 4	0 - 7
Eosinophils (%)	0 - 3	0 - 4
Basophils (%)	0	0 - 1

*Values were obtained from control rats (approximately 35 of each sex) from other subacute studies at SRI with Sprague-Dawley rats conducted at Peninsula Medical Laboratory.

Table B-6

RANGE OF CLINICAL CHEMISTRY VALUES IN RATS*

Parameter Examined	Males	Females
Glucose (mg %)	148 - 264	142 - 211
BUN (mg %)	13 - 26	14 - 25
Creatinine (mg %)	0.2 - 0.6	0.4 - 0.9
Uric acid (mg %)	1.1 - 3.9	1.1 - 3.3
Na+ (meq/l)	138 - 144	136 - 144
K+ (meq/l)	4.1 - 6.1	4.2 - 5.7
CO_2 (meq/l)	19 - 32	18 - 28
Cl^- (meq/l)	99 - 107	99 - 109
Ca^{2+} (mg %)	9.4 - 11.4	9.2 - 11.0
P (mg %)	5.3 - 10.0	4.3 - 8.9
Na-[Cl + CO_2]	10.00 - 17.00	9.00 - 17.00
Cholesterol (mg %)	38 - 83	56 - 89
Triglycerides (mg %)	74 - 282	20 - 216
Bilirubin (mg %)	0.1 - 0.2	0.1
SGOT (mu/ml)	126 - 419	109 - 266
SGPT (mu/ml)	34 - 124	25 - 62
LDH (mu/ml)	350 - 3700	800 - 2415
Alk P (mu/ml)	178 - 689	186 - 386
Iron (mcg %)	171 - 549	216 - 412
Total protein (g %)	5.6 - 6.5	5.4 - 6.8
Albumin (g %)	2.3 - 3.3	2.7 - 3.6
Globulin (g %)	2.3 - 3.5	2.6 - 3.7
A/G	0.80 - 1.17	0.76 - 1.19

*Values were obtained from control rats (approximately 35 of each sex) from subacute studies on other contracts at SRI with Sprague-Dawley rats. The tests were conducted at Peninsula Medical Laboratory.

TABLE B-7

POOLED STATISTICS FOR SUBACUTE DOG STUDIES AT SRI*

MALES

VARIABLE	N	MEAN	SE	NORMAL RANGE (± 2 S.D.)
INITIAL	60	9.63	.20	6.56 - 12.73
WEEK 1	15	9.58	.41	6.40 - 12.76
WEEK 2	15	9.73	.41	6.52 - 12.93
WEEK 3	15	9.79	.36	6.98 - 12.60
WEEK 4	15	9.97	.38	6.99 - 12.94
WEEK 5	13	9.94	.41	7.01 - 12.87
WEEK 6	13	9.98	.41	7.06 - 12.91
WEEK 7	13	10.11	.43	7.02 - 13.19
WEEK 8	13	10.31	.41	7.19 - 13.03
WEEK 9	11	10.47	.42	7.71 - 13.23
WEEK 10	11	10.54	.39	7.93 - 13.14
WEEK 11	11	10.64	.38	8.14 - 13.13
WEEK 12	11	10.66	.37	8.18 - 13.13
WEEK 13	11	10.78	.38	8.26 - 13.30
WEEK 14	6	10.33	.36	8.58 - 12.08
WEEK 15	6	10.32	.35	8.59 - 12.04
WEEK 16	6	10.27	.41	8.26 - 12.27
WEEK 17	6	10.43	.41	8.44 - 12.43
WEEK 18	5	10.58	.45	8.57 - 12.59
WEEK 19	5	10.74	.49	8.57 - 12.91
WEEK 20	5	10.70	.55	8.23 - 13.17
WEEK 21	5	10.64	.51	8.37 - 12.91
WEEK 22	5	10.56	.52	8.23 - 12.89
WEEK 23	5	10.54	.53	8.17 - 12.91
WEEK 24	5	10.18	.47	8.06 - 12.30
FINAL	13	10.80	.32	8.49 - 13.11
BRAIN	13	82.82	1.16	74.45 - 91.19
THYROID	13	107.63	4.18	77.50 -137.75
HEART	13	59.36	2.97	37.95 - 80.77
LIVER	13	395.13	21.95	236.84 -553.43
SPLEEN	13	31.70	2.71	12.14 - 51.27
ADRENAL	13	18.16	1.20	9.54 - 26.78
KIDNEYS	13	1.50	.12	.65 - 2.36
TESTES	13	.96	.08	.38 - 1.53
RBC	60	6.04	.07	5.01 - 7.07
HGB	60	16.45	.13	12.44 - 16.46
HCT	60	41.45	.43	34.77 - 48.13
MCV	60	68.52	.25	64.67 - 72.36
MCH	60	24.03	.16	21.61 - 26.45
MCHC	60	34.75	.33	29.66 - 39.84
WBC	60	12.08	.27	7.85 - 16.29
PMN	41	56.17	1.13	41.64 - 70.70
BANDS	41	1.31	.21	0.00 - 4.09
LYMPH	41	27.80	.93	15.17 - 39.90
MONO	41	5.43	.37	.68 - 10.17
EOSIN	41	8.33	.71	0.00 - 17.18
BASO	41	0.00	0.00	0.00 - 0.00
ATYP LYMPH	20	1.27	.22	0.00 - 3.21
RETIC	40	.74	.07	0.00 - 1.60
GLUCOSE	60	105.51	1.47	82.80 -128.22
BUN	60	14.62	.53	6.36 - 22.89
CREAT	60	.75	.01	.55 - .94
URIC ACID	60	.68	.06	0.00 - 1.58
NA	40	145.34	.35	140.88 -149.80
K	40	4.90	.05	4.32 - 5.48
CO2	40	21.69	.25	18.50 - 24.88
CL	40	109.81	2.32	80.43 -139.19
CA	40	11.11	.14	8.89 - 13.34
P	60	6.78	.38	.97 - 12.59
NA- (Cl + CO_2)	40	11.59	.35	7.20 - 15.98
CHOL	60	154.58	4.40	86.45 -222.70
TRIG	60	41.21	2.52	2.16 - 80.26
BILI	59	.24	.03	0.00 - .68
SGOT	60	35.05	1.18	16.76 - 53.33
SGPT	60	35.13	1.41	13.25 - 57.01
LDH	60	62.54	4.20	0.00 -127.65
ALK-P	60	116.10	6.28	18.75 -213.44
IRON	40	197.89	7.54	102.47 -293.30
PROTEIN	60	5.72	.06	4.79 - 6.65
ALBUMIN	60	3.60	.08	2.31 - 4.88
GLOBULIN	40	2.20	.12	.67 - 3.73
A/G RATIO	40	1.90	.16	0.00 - 3.91

*Over the period September 1976 through September 1978.

POOLED STATISTICS FOR SUBACUTE DOG STUDIES AT SRI*

FEMALES

VARIABLE	N	MEAN	SE	NORMAL RANGE (± 2 S.D.)
INITIAL	60	8.65	.20	5.60 - 11.69
WEEK 1	15	8.48	.37	5.63 - 11.33
WEEK 2	15	8.44	.34	5.79 - 11.09
WEEK 3	15	8.46	.33	5.89 - 11.03
WEEK 4	15	8.65	.35	5.96 - 11.33
WEEK 5	13	8.53	.35	6.00 - 11.06
WEEK 6	13	8.55	.35	6.04 - 11.06
WEEK 7	13	8.67	.35	6.18 - 11.16
WEEK 8	13	8.65	.35	6.12 - 11.19
WEEK 9	11	8.71	.38	6.19 - 11.23
WEEK 10	11	8.73	.39	6.14 - 11.31
WEEK 11	11	8.76	.39	6.19 - 11.34
WEEK 12	11	8.73	.37	6.25 - 11.20
WEEK 13	11	8.85	.38	6.33 - 11.38
WEEK 14	6	8.43	.47	6.15 - 10.72
WEEK 15	6	8.38	.51	5.86 - 10.90
WEEK 16	6	8.40	.56	5.67 - 11.13
WEEK 17	6	8.32	.52	5.76 - 10.87
WEEK 18	5	8.42	.70	5.30 - 11.54
WEEK 19	5	8.36	.65	5.46 - 11.26
WEEK 20	5	8.36	.69	5.29 - 11.43
WEEK 21	5	8.42	.69	5.35 - 11.49
WEEK 22	5	8.16	.68	5.12 - 11.20
WEEK 23	5	8.22	.67	5.23 - 11.21
WEEK 24	5	8.08	.68	5.03 - 11.13
FINAL	13	8.88	.35	6.35 - 11.41
BRAIN	13	80.38	1.29	71.08 - 89.67
THYROID	13	87.01	2.76	67.08 -106.93
HEART	13	43.46	1.40	33.36 - 53.56
LIVER	13	325.00	14.82	218.14 -431.86
SPLEEN	13	33.82	4.75	0.00 - 68.06
ADRENAL	13	1.49	.20	.05 - 2.92
KIDNEYS	13	1.39	.07	.92 - 1.86
TESTES	13	1.03	.07	.55 - 1.50
RBC	60	6.33	.08	5.07 - 7.59
HGB	60	15.32	.16	12.77 - 17.87
HCT	60	43.69	.54	35.28 - 52.09
MCV	60	68.76	.21	65.57 - 71.95
MCH	60	24.19	.16	21.72 - 26.66
MCHC	60	35.05	.20	31.96 - 38.14
WBC	60	12.03	.30	7.39 - 16.67
PMN	41	58.49	1.18	43.42 - 73.55
BANDS	41	1.59	.56	0.00 - 8.64
LYMPH	41	26.70	1.14	12.13 - 41.29
MONO	41	9.80	1.48	0.00 - 28.75
EOSIN	41	8.25	1.00	0.00 - 20.88
BASO	41	0.00	0.00	0.00 - 0.00
ATYP LYMPH	20	.94	.24	0.00 - 3.12
RETIC	40	.72	.10	0.00 - 1.93
GLUCOSE	60	106.31	1.35	85.38 -127.25
BUN	60	15.26	.55	6.71 - 23.81
CREAT	60	.75	.01	.56 - .94
URIC ACID	60	.67	.06	0.00 - 1.58
NA	40	146.39	.27	143.02 -149.75
K	40	4.74	.04	4.26 - 5.21
CO2	40	22.04	.26	18.78 - 25.30
CL	40	111.77	.25	108.58 -114.97
CA	60	11.24	.12	9.43 - 13.06
P	60	6.59	.35	1.24 - 11.94
NA-(Cl + CO_2)	40	12.57	.31	8.71 - 16.44
CHOL	60	153.94	4.26	87.89 -219.99
TRIG	60	40.80	2.42	3.31 - 78.29
BILI	60	.25	.03	0.00 - .67
SGOT	60	33.48	.91	19.61 - 47.55
SGPT	60	30.43	1.24	11.21 - 49.65
LDH	60	53.51	3.79	0.00 -112.16
ALK-P	60	98.36	4.34	31.15 -165.57
IRON	40	188.95	7.81	90.14 -287.77
PROTEIN	60	5.69	.05	4.87 - 6.50
ALBUMIN	60	3.73	.08	2.47 - 4.98
GLOBULIN	40	2.11	.12	.60 - 3.61
A/G RATIO	40	2.11	.18	0.00 - 4.36

*Over the period September 1976 through September 1978.

TABLE B-9

POOLED STATISTICS FOR SUBACUTE RAT STUDIES AT SRI

MALES

VARIABLE	N	MEAN	SE	NORMAL RANGE (± 2 S.D.)
INITIAL	70	151.41	1.93	119.19 - 183.64
WEEK 1	70	200.41	2.67	155.68 - 245.15
WEEK 2	69	252.96	2.47	211.89 - 294.03
WEEK 3	69	291.77	2.69	247.15 - 336.39
WEEK 4	69	324.23	3.12	272.32 - 376.15
WEEK 5	50	348.58	4.01	291.85 - 405.31
WEEK 6	50	369.46	4.06	312.01 - 426.91
WEEK 7	50	390.32	4.77	322.79 - 457.85
WEEK 8	50	410.44	5.33	335.02 - 485.86
WEEK 9	40	425.95	6.49	343.86 - 508.04
WEEK 10	40	443.02	6.41	361.93 - 524.12
WEEK 11	40	453.20	7.20	362.17 - 544.23
WEEK 12	40	462.97	8.10	360.56 - 565.39
WEEK 13	40	465.47	9.51	345.24 - 585.71
WEEK 14	10	487.40	13.51	401.96 - 572.84
WEEK 15	10	498.80	15.21	402.58 - 595.02
WEEK 16	10	502.90	14.30	412.46 - 593.34
WEEK 17	10	486.20	13.58	400.32 - 572.08
BRAIN	69	2.17	.02	1.79 - 2.55
HEART	69	1.52	.04	.87 - 2.17
KIDNEYS	69	3.31	.07	2.07 - 4.54
LIVER	69	14.17	.38	7.94 - 20.40
SPLEEN	69	.75	.02	.47 - 1.02
TESTES	69	3.35	.08	2.03 - 4.68
RBC	62	7.72	.09	6.33 - 9.12
HGB	62	14.97	.11	13.20 - 16.74
HCT	62	40.67	.37	34.81 - 46.53
MCV	62	53.27	.43	46.53 - 60.02
MCH	62	19.50	.22	16.09 - 22.92
MCHC	62	36.89	.38	30.92 - 42.87
WBC	62	8.30	.34	2.89 - 13.70
PMN	62	15.84	.70	4.82 - 26.86
BANDS	62	.37	.09	0.00 - 1.83
LYMPH	62	79.16	.77	67.04 - 91.28
MONO	52	3.48	.25	0.00 - 7.08
EOSIN	34	1.35	.10	.16 - 2.55
BASO	63	0.00	0.00	0.00 - 0.00
ATYP LYMPH	25	2.04	.33	0.00 - 5.38
RETIC	25	.94	.15	0.00 - 2.44
GLUCOSE	66	152.94	4.35	82.24 - 223.64
BUN	66	18.18	.53	9.64 - 26.72
CREAT	64	.59	.02	.31 - .87
URIC ACID	61	1.85	.14	0.00 - 4.01
NA	36	143.92	.42	138.85 - 148.98
K	64	6.34	.23	2.65 - 10.03
CO2	36	24.50	.58	17.56 - 31.44
CL	36	102.33	.47	96.74 - 107.93
CA	55	9.38	.10	7.97 - 10.79
P	36	6.24	.16	4.27 - 8.20
NA-(Cl + CO_2)	36	17.08	.74	8.19 - 25.98
CHOL	64	45.77	3.06	0.00 - 94.69
TRIG	64	95.91	8.87	0.00 - 237.87
BILI	59	.32	.04	0.00 - .88
SGOT	66	107.38	4.45	35.04 - 179.71
SGPT	66	37.67	1.48	13.54 - 61.79
LDH	61	785.82	65.57	0.00 - 1810.00
ALK-P	57	204.19	12.53	14.98 - 393.41
IRON	36	194.25	7.34	106.14 - 282.36
PROTEIN	64	6.24	.08	5.02 - 7.47
ALBUMIN	64	4.46	.12	2.52 - 6.40
GLOBULIN	36	1.81	.21	0.00 - 4.35
A/G RATIO	36	5.91	1.06	0.00 - 18.55

TABLE B-10

POOLED STATISTICS FOR SUBACUTE RAT STUDIES AT SRI

FEMALES

VARIABLE	N	MEAN	SE	NORMAL RANGE (± 2 S.D.)
INITIAL	70	151.91	2.13	116.27 - 187.56
WEEK 1	70	175.39	1.32	153.30 - 197.47
WEEK 2	70	196.63	1.30	174.95 - 218.31
WEEK 3	70	210.70	1.46	186.30 - 235.10
WEEK 4	70	222.91	1.60	196.22 - 249.61
WEEK 5	50	233.62	2.06	204.49 - 262.75
WEEK 6	50	244.50	2.39	210.64 - 278.36
WEEK 7	50	250.90	2.66	213.35 - 288.45
WEEK 8	50	258.92	2.74	220.14 - 297.70
WEEK 9	40	266.02	3.43	222.65 - 309.40
WEEK 10	40	273.85	3.85	225.10 - 322.60
WEEK 11	40	277.95	4.04	226.81 - 329.09
WEEK 12	40	282.30	3.60	236.71 - 327.89
WEEK 13	40	281.90	3.66	235.57 - 328.23
WEEK 14	10	274.40	4.39	246.62 - 302.18
WEEK 15	10	278.10	4.31	250.87 - 305.33
WEEK 16	10	279.20	4.41	251.33 - 307.07
WEEK 17	10	270.00	4.40	242.18 - 297.82
BRAIN	70	2.02	.02	1.74 - 2.31
HEART	70	1.02	.02	.61 - 1.43
KIDNEYS	70	1.93	.03	1.42 - 2.44
LIVER	70	8.00	.16	5.26 - 10.73
SPLEEN	70	.56	.01	.36 - .76
RBC	67	7.35	.07	6.20 - 8.50
HGB	67	14.80	.12	12.91 - 16.68
HCT	67	39.42	.42	32.61 - 46.23
MCV	67	54.24	.22	50.60 - 57.88
MCH	68	19.84	.35	13.99 - 25.68
MCHC	67	37.64	.38	31.42 - 43.87
WBC	67	6.77	.28	2.27 - 11.28
PMN	67	15.75	1.07	0.00 - 33.28
BANDS	66	.39	.10	0.00 - 2.07
LYMPH	67	79.84	1.08	62.10 - 97.57
MONO	50	3.22	.24	0.00 - 6.68
EOSIN	31	2.00	.26	0.00 - 4.92
BASO	70	0.00	0.00	0.00 - 0.00
ATYP LYMPH	30	1.60	.21	0.00 - 3.87
RETIC	30	1.04	.15	0.00 - 2.66
GLUCOSE	65	147.15	3.35	93.08 - 201.23
BUN	65	18.38	.61	8.60 - 28.17
CREAT	63	.60	.01	.37 - .82
URIC ACID	59	1.86	.12	0.00 - 3.78
NA	33	142.03	.51	136.17 - 147.89
K	63	6.10	.21	2.72 - 9.48
CO2	33	21.85	.66	14.31 - 29.38
CL	33	103.70	.53	97.60 - 109.79
CA	53	10.19	.15	8.06 - 12.33
P	33	5.40	.23	2.80 - 8.00
NA- (Cl + CO_2)	33	16.48	.65	8.97 - 24.00
CHOL	63	64.19	1.93	33.49 - 94.89
TRIG	63	57.51	5.82	0.00 - 149.90
BILI	63	.34	.04	0.00 - .94
SGOT	65	101.15	6.35	0.00 - 203.52
SGPT	65	34.88	2.50	0.00 - 75.24
LDH	64	608.80	46.65	0.00 -1355.14
ALK-P	55	131.16	9.38	0.00 - 270.35
IRON	33	339.42	11.94	202.29 - 476.56
PROTEIN	63	6.60	.09	5.13 - 8.06
ALBUMIN	63	4.75	.14	2.50 - 6.99
GLOBULIN	30	1.96	.23	0.00 - 4.53
A/G RATIO	30	5.51	1.17	0.00 - 18.30

TABLE B-11

POOLED STATISTICS FOR SUBACUTE MOUSE STUDIES AT SRI

MALES

VARIABLE	N	MEAN	SE	NORMAL RANGE (± 2 S.D.)
INITIAL	60	23.17	.37	17.45 - 28.89
WEEK 1	60	24.83	.49	17.29 - 32.38
WEEK 2	59	25.75	.55	17.31 - 34.18
WEEK 3	58	26.24	.64	16.56 - 35.93
WEEK 4	57	29.07	.52	21.15 - 36.99
WEEK 5	47	30.79	.58	22.89 - 38.69
WEEK 6	47	31.70	.55	24.19 - 39.22
WEEK 7	47	31.98	.63	23.36 - 40.60
WEEK 8	47	34.55	.66	25.52 - 43.58
WEEK 9	37	33.97	.68	25.68 - 42.27
WEEK 10	37	34.43	.69	26.05 - 42.82
WEEK 11	37	35.41	.67	27.25 - 43.56
WEEK 12	37	36.00	.66	27.93 - 44.07
WEEK 13	37	36.05	.69	27.66 - 44.45
WEEK 14	10	38.20	.99	31.96 - 44.44
WEEK 15	10	39.60	1.02	33.12 - 46.08
WEEK 16	10	38.90	.91	33.13 - 44.67
WEEK 17	10	38.10	.86	32.65 - 43.55
BRAIN	57	.53	.01	.44 - .62
HEART	57	.19	.01	.11 - .27
KIDNEYS	57	.55	.01	.33 - .78
LIVER	57	1.87	.06	1.00 - 2.74
SPLEEN	57	.12	.01	.04 - .20
TESTES	57	.26	.01	.15 - .38
RBC	47	7.77	.18	5.37 - 10.18
HGB	47	13.96	.23	10.80 - 17.11
HCT	47	39.40	.86	27.66 - 51.14
MCV	47	50.96	.45	44.74 - 57.17
MCH	47	18.28	.29	14.37 - 22.19
MCHC	47	36.09	.62	27.57 - 44.60
WBC	47	6.59	.50	0.00 - 13.49
PMN	45	21.27	1.43	2.06 - 40.48
BANDS	46	.15	.07	0.00 - 1.09
LYMPH	46	73.39	1.66	50.84 - 95.95
MONO	46	2.35	.32	0.00 - 6.71
EOSIN	46	1.67	.26	0.00 - 5.25
BASO	46	0.00	0.00	0.00 - 0.00
ATYP LYMPH	29	1.97	.37	0.00 - 5.98
RETIC	30	1.40	.24	0.00 - 4.01

TABLE B-12

POOLED STATISTICS FOR SUBACUTE MOUSE STUDIES AT SRI

FEMALES

VARIABLE	N	MEAN	SE	NORMAL RANGE (± 2 S.D.)
INITIAL	60	22.05	.35	16.66 - 27.44
WEEK 1	60	22.95	.44	16.20 - 29.70
WEEK 2	60	23.38	.47	16.04 - 30.73
WEEK 3	60	23.70	.56	15.01 - 32.39
WEEK 4	59	25.41	.53	17.24 - 33.58
WEEK 5	49	25.90	.56	18.01 - 33.79
WEEK 6	49	26.73	.63	17.94 - 35.53
WEEK 7	49	27.92	.55	20.28 - 35.55
WEEK 8	48	28.19	.55	20.52 - 35.86
WEEK 9	38	28.97	.64	21.12 - 36.83
WEEK 10	38	28.66	.62	20.97 - 36.34
WEEK 11	38	29.29	.57	22.25 - 36.32
WEEK 12	38	29.11	.77	19.65 - 38.56
WEEK 13	38	30.05	.68	21.62 - 38.49
WEEK 14	9	30.56	1.59	21.01 - 40.10
WEEK 15	9	32.00	1.61	22.36 - 41.64
WEEK 16	9	31.67	1.53	22.50 - 40.83
WEEK 17	9	31.67	1.70	21.47 - 41.86
BRAIN	58	.53	.01	.41 - .65
HEART	58	.16	.01	.07 - .25
KIDNEYS	58	.41	.01	.26 - .57
LIVER	58	1.64	.05	.88 - 2.39
SPLEEN	58	.12	.00	.05 - .19
RBC	45	8.24	.20	5.52 - 10.97
HGB	45	14.69	.23	11.59 - 17.79
HCT	45	41.30	1.03	27.53 - 55.07
MCV	45	49.89	.41	44.44 - 55.34
MCH	45	18.08	.28	14.27 - 21.89
MCHC	45	36.27	.61	28.07 - 44.47
WBC	45	6.41	.43	.70 - 12.11
PMN	45	18.87	1.27	1.89 - 35.84
BANDS	44	.59	.23	0.00 - 3.62
LYMPH	45	76.09	1.39	57.42 - 94.76
MONO	45	1.67	.26	0.00 - 5.13
EOSIN	45	1.89	.36	0.00 - 6.77
BASO	45	.04	.04	0.00 - .64
ATYP LYMPH	28	1.75	.28	0.00 - 4.71
RETIC	28	1.36	.20	0.00 - 3.43

Appendix C

LINEAR TREND ANALYSIS

The data obtained from the subacute studies with TNT, LAP, and LAP(I) (Parts 2, 3, and 4) were analyzed statistically for linear trends. The linear trend test is a procedure for establishing the existence of a linear trend in the mean response among the dose-treated groups. More precisely, this test seeks to uncover linear trends as a function of the logarithm of the dose. To compute this test, a linear regression of response versus log dose is first computed (excluding the control group). This linear regression takes the form

$$Y_{ij} = a + b * \log d_i$$

where

Y_{ij} = response of j-th animals in the i-th dose group (e.g., weight, hematology, or clinical chemistry measurement)

d_i = dose administered to the i-th group.

An F test is used to test the hypothesis that $b = 0$. If the hypothesis can be rejected (e.g., a linear trend exists) at the 5% significance level (e.g., with 95% confidence), then a "*" is printed in the appropriate position on the summary table. If the hypothesis can be rejected at the 1% significance level (e.g., with 99% confidence), then a "+" is printed on the appropriate position in the summary table.

The results are summarized in Tables C-1 through C-28. The parameters analyzed were body weights and weight differences, organ weights and weight ratios, and hematological and clinical chemistry values.

LINEAR TREND ANALYSIS OF TNT EFFECTS ON DOG BODY WEIGHTS AND DIFFERENCES IN DOG BODY WEIGHTS

DEPENDENT	TABLE NUMBER							
VARIABLE	11	12	15	16	17	18	13	14
INITIAL		*						
WEEK 1								+
WEEK 2								
WEEK 3								
WEEK 4								
WEEK 5			*					
WEEK 6			*					
WEEK 7								
WEEK 8								
WEEK 9			-	-				
WEEK 10			-	-				
WEEK 11			-	-				
WEEK 12			-	-				
WEEK 13			-	-				
WEEK 14	-	-	-	-			-	-
WEEK 15	-	-	-	-			-	-
WEEK 16	-	-	-	-			-	-
WEEK 17	-	-	-	-			-	-

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-2

LINEAR TREND ANALYSIS OF TNT EFFECTS ON ORGAN WEIGHTS
AND WEIGHT RATIOS OF DOGS

DEPENDENT VARIABLE	TABLE NUMBER 21	22	23	24	27	28
FINAL WT(KG)						
BRAIN						
HEART		*				+
KIDNEYS		*				
LIVER				*		
SPLEEN						
GONADS						
ADRENAL					*	
THYROID						
BRAIN/BODY						
HEART/BODY						+
KIDNEY/BODY						
LIVER/BODY				+		
SPLEEN/BODY						
GONAD/BODY						
ADRENAL/BODY						
THYROID/BODY						
HEART/BRAIN					+	+
KIDNEY/BRAIN	*					
LIVER/BRAIN				*		*
SPLEEN/BRAIN						
GONAD/BRAIN		*				
ADRENAL/BRAIN						
THYROID/BRAIN						+

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-3

LINEAR TREND ANALYSIS OF TNT EFFECTS ON HEMATOLOGY OF DOGS

DEPENDENT	TABLE NUMBER											
VARIABLE	29	30	31	32	33	34	35	36	37	38	39	40
RBC			+	+	*	+	*					
HGB			+	+	*	+	*					
HCT			+	+		*						
MCV		+	+	+	*		*					
MCH												
MCHC			+	+		+	*	+		*		
WBC								*	*			
PMN			+	+		+						
BANDS			+	+		+		*				
LYMPH												
MONO			+	*				+				
EOSIN										+		+
BASO												

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-4

LINEAR TREND ANALYSIS OF TNT EFFECTS ON CLINICAL CHEMISTRY OF DOGS

DEPENDENT VARIABLE	TABLE NUMBER 41	42	43	44	45	46	47	48	49	50	51	52
GLUCOSE			*									
BUN			*		*		*		*			
CREAT					*							
URIC ACID												
NA				+								
K											+	
CO_2					*							
CL												
CA												
P												
NA- $(CL + CO_2)$		*	+									
CHOL			+		*						+	
TRIG			*								+	
BILI	*							+				
SGOT		*								+		
SGPT			+		+	+	+	+				
LDH												
ALK-P				*								
IRON			*	*								
PROTEIN					*							
ALBUMIN				+			*					
GLOBULIN					*							
A/G				*			*					

LINEAR TREND TESTS OF LOG DOSES
\+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
\- VARIABLE NOT INCLUDED IN TABLE

TABLE C-5

LINEAR TREND ANALYSIS OF TNT EFFECTS ON RAT BODY WEIGHTS

DEPENDENT VARIABLE	TABLE NUMBER 59	60	63	64	65	66
INITIAL		+				
WEEK 1	+	+	+	+	+	+
WEEK 2	+	+	+	*	+	+
WEEK 3	+	+	+	*	+	+
WEEK 4	+	+	+	+	+	+
WEEK 5	+	+	+		+	*
WEEK 6	+	+	+	*	+	+
WEEK 7	+	+	+	*	*	+
WEEK 8	+	+	+		*	+
WEEK 9	+	+	-	-	*	*
WEEK 10	+	+	-	-	*	+
WEEK 11	+	+	-	-	*	+
WEEK 12	+	+	-	-	*	+
WEEK 13	+	+	-	-	*	+
WEEK 14	-	-	-	-		*
WEEK 15	-	-	-	-		*
WEEK 16	-	-	-	-		
WEEK 17	-	-	-	-		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-6

LINEAR TREND ANALYSIS OF TNT EFFECTS ON DIFFERENCES IN RAT BODY WEIGHTS

DEPENDENT	TABLE NUMBER					
VARIABLE	61	62	67	68	69	70
WEEK 1	+	+	+	+	+	+
WEEK 2	+		+			
WEEK 3						
WEEK 4	+	+	*	+		*
WEEK 5			+	+		
WEEK 6	+		*	*	*	
WEEK 7						
WEEK 8				*		
WEEK 9	+	+	-	-	*	+
WEEK 10	+	+	-	-	+	+
WEEK 11			-	-		
WEEK 12			-	-		
WEEK 13			-	-	+	
WEEK 14	-	-	-	-	+	+
WEEK 15	-	-	-	-		*
WEEK 16	-	-	-	-	+	
WEEK 17	-	-	-	-		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-7

LINEAR TREND ANALYSIS OF TNT EFFECTS ON ORGAN WEIGHTS AND WEIGHT RATIOS OF RATS

DEPENDENT	TABLE NUMBER							
VARIABLE	85	89	87	91	86	90	88	92
FINAL WT	+		+		+		+	
BRAIN				*				+
HEART								+
KIDNEYS							*	+
LIVER	+							+
SPLEEN	+		+	*	+		+	+
TESTES	+	+	+	+				
BRAIN/BODY			+		+		+	*
HEART/BODY					+		+	+
KIDNEY/BODY	+				*		*	+
LIVER/BODY	+		+		+		+	+
SPLEEN/BODY	+		+	+	+		+	+
TESTES/BODY	+	+	+	+				
HEART/BRAIN				*				*
KIDNEY/BRAIN								*
LIVER/BRAIN	+							*
SPLEEN/BRAIN	+		+		+		+	*
TESTES/BRAIN	+	+	+	+				

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-8

LINEAR TREND ANALYSIS OF TNT EFFECTS ON HEMATOLOGY OF RATS

DEPENDENT	TABLE NUMBER							
VARIABLE	93	94	97	98	95	96	99	100
RBC	+	+			+	+		
HGB	+	+			+	+	+	
HCT	+	+	*		+	+	+	
MCV		+		*	+	*	+	
MCH		*			+	*	+	
MCHC	*	+	+		+	+	*	*
WBC	+					+		
PMN						*	*	
BANDS								
LYMPH						*	*	
MONO		*						
EOSIN								
BASO								

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-9

LINEAR TREND ANALYSIS OF TNT EFFECTS ON CLINICAL CHEMISTRY OF RATS

DEPENDENT VARIABLE	TABLE NUMBER 101	102	105	106	103	104	107	108
GLUCOSE		*			+			
BUN	*							*
CREAT	+	+						+
URIC ACID							-	-
NA	*						*	
K		+						
CO2			*					
CL	*							
CA			+					
P								*
NA- (CL + CO_2)			+				+	*
CHOL	+	+	*		+	+	+	
TRIG					+		-	
BILI			+	+	+	+	*	
SGOT								
SGPT	+	+			+	+		*
LDH			*	*		+		
ALK-P					+			
IRON		*	*		*			
PROTEIN		*		*				
ALBUMIN							+	+
GLOBULIN		*	+	*	*		+	*
A/G		*	*	*			+	

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-10

LINEAR TREND ANALYSIS OF TNT EFFECTS ON MICE BODY WEIGHTS

DEPENDENT VARIABLE	TABLE NUMBER 117	118	121	122	123	124
INITIAL						
WEEK 1	*	+		+	+	
WEEK 2		+			+	
WEEK 3		+			*	*
WEEK 4						*
WEEK 5		+	*			*
WEEK 6		+				*
WEEK 7		*				*
WEEK 8		+	*			*
WEEK 9		+	-	-		+
WEEK 10			-	-		
WEEK 11		+	-	-		*
WEEK 12		*	-	-		*
WEEK 13		*	-	-		
WEEK 14	-	-	-	-		*
WEEK 15	-	-	-	-		*
WEEK 16	-	-	-	-		
WEEK 17	-	-	-	-		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-11

LINEAR TREND ANALYSIS OF TNT EFFECTS ON DIFFERENCES IN MICE BODY WEIGHTS

DEPENDENT	TABLE NUMBER					
VARIABLE	119	120	125	126	127	128
WEEK 1	+	+		+	*	*
WEEK 2		*				
WEEK 3	*					+
WEEK 4	+	+	+	+		
WEEK 5	*		*			
WEEK 6						
WEEK 7					+	
WEEK 8		*		*		
WEEK 9			-	-		*
WEEK 10	+	*	-	-	+	+
WEEK 11			-	-		+
WEEK 12		*	-	-	+	
WEEK 13			-	-	+	
WEEK 14	-	-	-	-		
WEEK 15	-	-	-	-		
WEEK 16	-	-	-	-		+
WEEK 17	-	-	-	-		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-12

LINEAR TREND ANALYSIS OF TNT EFFECTS ON ORGAN WEIGHTS AND WEIGHT RATIOS OF MICE

DEPENDENT VARIABLE	143	147	145	149	144	148	146	150
FINAL WT		*						
BRAIN								
HEART								
KIDNEYS	*	*		*	+	*		
LIVER	*	*		+				
SPLEEN					*	*		
TESTES	*							
BRAIN/BODY		+						
HEART/BODY		*						
KIDNEY/BODY								
LIVER/BODY	+			+		*		
SPLEEN/BODY					+	*		
TESTES/BODY								
HEART/BRAIN								
KIDNEY/BRAIN		*		*	*			
LIVER/BRAIN	*	*		+			*	
SPLEEN/BRAIN					*	*		
TESTES/BRAIN	*							

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-13

LINEAR TREND ANALYSIS OF TNT EFFECTS ON HEMATOLOGY OF MICE

DEPENDENT	TABLE NUMBER							
VARIABLE	151	152	155	156	153	154	157	158
RBC	*							
HGB								
HCT							*	
MCV	+							+
MCH	+				*			
MCHC	*						*	*
WBC				*				
PMN					+			*
BANDS					*			
LYMPH		*			*			*
MONO					*	+		
EOSIN		*						
BASO								

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-14

LINEAR TREND ANALYSIS OF LAP EFFECTS ON DOG BODY WEIGHTS AND DIFFERENCES IN DOG BODY WEIGHTS

DEPENDENT	TABLE NUMBER							
VARIABLE	167	168	171	172	169	170	173	174
INITIAL								
WEEK 1					*	+		
WEEK 2		*	+		*	+		
WEEK 3		+						
WEEK 4	*	*						
WEEK 5								
WEEK 6								
WEEK 7								
WEEK 8								
WEEK 9			-	-		*	-	-
WEEK 10			-	-			-	-
WEEK 11			-	-			-	-
WEEK 12			-	-			-	-
WEEK 13			-	-			-	-

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-15

LINEAR TREND ANALYSIS OF LAP EFFECTS ON ORGAN WEIGHTS AND WEIGHT RATIOS OF DOGS

DEPENDENT VARIABLE	TABLE NUMBER 177	178	181	182	179	180
FINAL WT(KG)						
BRAIN						
HEART		*				
KIDNEYS						
LIVER					*	
SPLEEN						
GONADS						
ADRENAL						
THYROID						
BRAIN/BODY						
HEART/BODY						
KIDNEY/BODY					*	
LIVER/BODY					*	*
SPLEEN/BODY						
GONAD/BODY						
ADRENAL/BODY						
THYROID/BODY						
HEART/BRAIN		+				
KIDNEY/BRAIN						*
LIVER/BRAIN					*	*
SPLEEN/BRAIN						
GONAD/BRAIN						
ADRENAL/BRAIN	*					
THYROID/BRAIN						

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-16

LINEAR TREND ANALYSIS OF LAP EFFECTS ON HEMATOLOGY OF DOGS

DEPENDENT VARIABLE	TABLE NUMBER 183	184	185	186	187	188	189	190
RBC			+	+	*	*		
HGB			+	+				
HCT			*	+				
MCV				*	*		*	*
MCH							+	
MCHC			*	+	*			
WBC					*		*	*
PMN					*		+	
BANDS								
LYMPH					*			
MONO							*	
EOSIN				*	+			
BASO								
RETIC				+		*	+	+

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-17

LINEAR TREND ANALYSIS OF LAP EFFECTS ON CLINICAL CHEMISTRY OF DOGS

DEPENDENT VARIABLE	TABLE NUMBER 193	194	195	196	197	198	199	200
GLUCOSE					*			
BUN				+				
CREAT		*	+	+				*
URIC ACID				*	*			
NA								
K			*	*				
CO2				*				
CL								
CA								*
P								
NA- (CL + CO_2)								
CHOL								
TRIG			*	+	+	*	*	
BILI					*	*		*
SGOT						*		
SGPT				+	*	+	+	
LDH		*						
ALK-P								
IRON			+					
PROTEIN		*	*					
ALBUMIN								
GLOBULIN			+					
A/G			*					

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-18

LINEAR TREND ANALYSIS OF LAP EFFECTS ON RAT BODY WEIGHTS AND DIFFERENCES IN BODY WEIGHTS

DEPENDENT	TABLE NUMBER			
VARIABLE	209	210	211	212
INITIAL				
WEEK 1	+	+	+	+
WEEK 2	+	+	+	
WEEK 3	+	+	+	+
WEEK 4	+	+	+	*
WEEK 5	+	+		
WEEK 6	+	+		
WEEK 7	+	+	*	+
WEEK 8	+	+		+
WEEK 9	+	+	+	+
WEEK 10	+	+		
WEEK 11	+	+		
WEEK 12	+	+		
WEEK 13	+	+		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-19

LINEAR TREND ANALYSIS OF LAP EFFECTS ON ORGAN WEIGHTS AND WEIGHT RATIOS OF RATS

DEPENDENT VARIABLE	TABLE NUMBER 219	220
FINAL WT	+	+
BRAIN		
HEART	+	+
KIDNEYS	*	+
LIVER		+
SPLEEN	+	+
TESTES	+	
BRAIN/BODY	+	+
HEART/BODY		
KIDNEY/BODY	+	+
LIVER/BODY	+	+
SPLEEN/BODY	+	+
TESTES/BODY		
HEART/BRAIN	+	+
KIDNEY/BRAIN	*	+
LIVER/BRAIN		+
SPLEEN/BRAIN	+	+
TESTES/BRAIN	+	

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-20

LINEAR TREND ANALYSIS OF LAP EFFECTS ON
HEMATOLOGY OF RATS

DEPENDENT VARIABLE	TABLE NUMBER 221	222
RBC	+	+
HGB	+	+
HCT	+	+
MCV	+	+
MCH		*
MCHC		
WBC		
PMN		
BANDS		
LYMPH		
MONO		
EOSIN		
BASO		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-21

LINEAR TREND ANALYSIS OF LAP EFFECTS ON
CLINICAL CHEMISTRY OF RATS

DEPENDENT VARIABLE	TABLE NUMBER 223	224
GLUCOSE		+
BUN		+
CREAT	*	
URIC ACID		
NA		
K		*
CO2		
CL		
CA	*	*
P		+
NA- (CL + CO_2)		
CHOL	+	+
TRIG	*	
BILI		+
SGOT	+	
SGPT		
LDH		
ALK-P		*
IRON		+
PROTEIN		
ALBUMIN		
GLOBULIN	*	
A/G	*	

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE
#
#FILE (WALTER)T72

TABLE C-22

LINEAR TREND ANALYSIS OF LAP EFFECTS ON MICE BODY WEIGHTS AND DIFFERENCES IN BODY WEIGHTS

DEPENDENT VARIABLE	TABLE NUMBER 227	228	229	230
INITIAL	+			
WEEK 1	+	+	+	+
WEEK 2	+	+	+	+
WEEK 3	+	+		
WEEK 4	+	+		
WEEK 5	+	+		
WEEK 6	+	+		
WEEK 7	+	*		+
WEEK 8	+	+	*	
WEEK 9	+	+	*	+
WEEK 10	+	+		+
WEEK 11	+	+		
WEEK 12	+	+		
WEEK 13	+	*		+

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-23

LINEAR TREND ANALYSIS OF LAP EFFECTS ON ORGAN WEIGHTS AND WEIGHT RATIOS OF MICE

DEPENDENT VARIABLE	TABLE NUMBER 255	256
FINAL WT	+	*
BRAIN	+	+
HEART	+	
KIDNEYS	+	+
LIVER		
SPLEEN		+
TESTES		
BRAIN/BODY	+	
HEART/BODY		
KIDNEY/BODY		+
LIVER/BODY	+	+
SPLEEN/BODY	+	+
TESTES/BODY	+	
HEART/BRAIN	+	
KIDNEY/BRAIN	+	+
LIVER/BRAIN		+
SPLEEN/BRAIN		+
TESTES/BRAIN	*	

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-24

LINEAR TREND ANALYSIS OF LAP EFFECTS
ON HEMATOLOGY OF MICE

DEPENDENT	TABLE NUMBER	
VARIABLE	239	240
RBC	+	+
HGB	*	+
HCT	+	+
MCV	*	
MCH	+	+
MCHC		*
WBC	+	*
PMN	+	
BANDS	+	+
LYMPH	+	
MONO		*
EOSIN		
BASO		
ATYP LYMPH		
RETIC	+	+

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE
#
#FILE (WALTER)T64

TABLE C-25

LINEAR TREND ANALYSIS OF LAP(I) EFFECTS
ON RAT BODY WEIGHTS AND WEIGHT DIFFERENCES

DEPENDENT VARIABLE	TABLE NUMBER 245	246	247	248
INITIAL				
WEEK 1	+	+	+	+
WEEK 2	+	+	+	
WEEK 3		+		
WEEK 4		+		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-26

LINEAR TREND ANALYSIS OF LAP(I) EFFECTS ON
ORGAN WEIGHTS AND WEIGHT RATIOS OF RATS

DEPENDENT VARIABLE	TABLE NUMBER 255	256
FINAL WT		+
BRAIN		
HEART		
LIVER		
SPLEEN		
KIDNEYS		
TESTES		
BRAIN/BODY		+
HEART/BODY		
LIVER/BODY	*	*
SPLEEN/BODY		
KIDNEY/BODY		+
TESTES/BODY		
HEART/BRAIN		
LIVER/BRAIN		
SPLEEN/BRAIN		
KIDNEY/BRAIN		
TESTES/BRAIN		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-27

LINEAR TREND ANALYSIS OF LAP(I) EFFECTS ON HEMATOLOGY OF RATS

DEPENDENT VARIABLE	TABLE NUMBER 257	258
RBC		
HGB		
HCT	*	
MCV	+	
MCH		
MCHC		*
WBC	+	
PMN		*
BANDS		
LYMPH		*
ATYP LYMP	+	
MONO		
EOSIN	*	
BASO		
RETIC		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE

TABLE C-28

LINEAR TREND ANALYSIS OF LAP(I) EFFECTS
ON CLINICAL CHEMISTRY OF RATS

DEPENDENT VARIABLE	TABLE NUMBER 259	260
ALBUMIN		
ALK-P		
BUN		
CA		
CHOL		
CREAT		
GLUC		
P		
LDH		
TRIG		
URIC ACID		
PROTEIN		
SGPT		*
SGOT		
BILI		

LINEAR TREND TESTS OF LOG DOSES
+ CONFIDENCE LEVEL = .99
* CONFIDENCE LEVEL = .95
- VARIABLE NOT INCLUDED IN TABLE
#

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